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CHRONIC PACHYMENINGITIS

Report of a Case and Review of the Literature

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CHRONIC pachymeningitis involving the dura of the posterior fossa and upper cervical regions and simulating intracranial tumor is of such rare occurrence as to prompt this report. The confusion regarding etiology and the inclusion in the literature of conditions which are not primarily inflammatory have stimulated this review. Of recent years this condition, popularized by Virchow, has received scant attention.

REPORT OF CASE

A. W., aged 40, a school teacher, first entered the University of California Hospital on Sept. 11, 1945, with the chief complaint of pain in the neck and headache since the fall of 1942.

Present Illness.—In September 1942, the patient had a five day episode of swelling of the neck and tenderness in both mastoid regions. In October of the same year she had a nonspecific infection termed "flu" accompanied with stiffness of the neck, headache and a temperature of 105 F. Sulfonamide treatment was given for four days; improvement was gradual, and the patient returned to work in four weeks. After this febrile episode the patient had intermittent attacks of occipital headaches and stiffness of the neck until April 1943, at which time a second febrile attack occurred. An abbreviated course of sulfonamide therapy was administered. Local washings of the sinuses were done, and physical therapy was administered to the neck; minimal relief was obtained. During the remainder of 1943 and throughout 1944 there was a gradual increase in frequency of headache and pain and stiffness of the neck. The pain was occipital in location, sudden in onset, associated with movement of the neck and brief in duration, lasting ten to fifteen minutes. Between these acute pains there were recurrent headaches of varying intensity in the temporal and mastoid regions. In May 1945, traction on the neck and injections into the occipital nerve gave no relief. In the five month period just prior to her entrance into the University Hospital, the patient noted blurring of vision and double vision, particularly at the peak of the headaches, occasionally associated with visions of black and white dots and orange and black streamers. After the acute attacks of pain in the head, tingling in all four extremities, especially in the fingers and fore-

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arms, was experienced. Two months prior to entry the patient had a third acute illness, with stiffness of the neck, swelling about the mastoid regions and tenderness in these general areas. A streptococcic infection of the throat was diagnosed and treated with penicillin. The cervical pain and headache became constant and remained so until her entry into the hospital.

Family History.—The family history was not relevant.

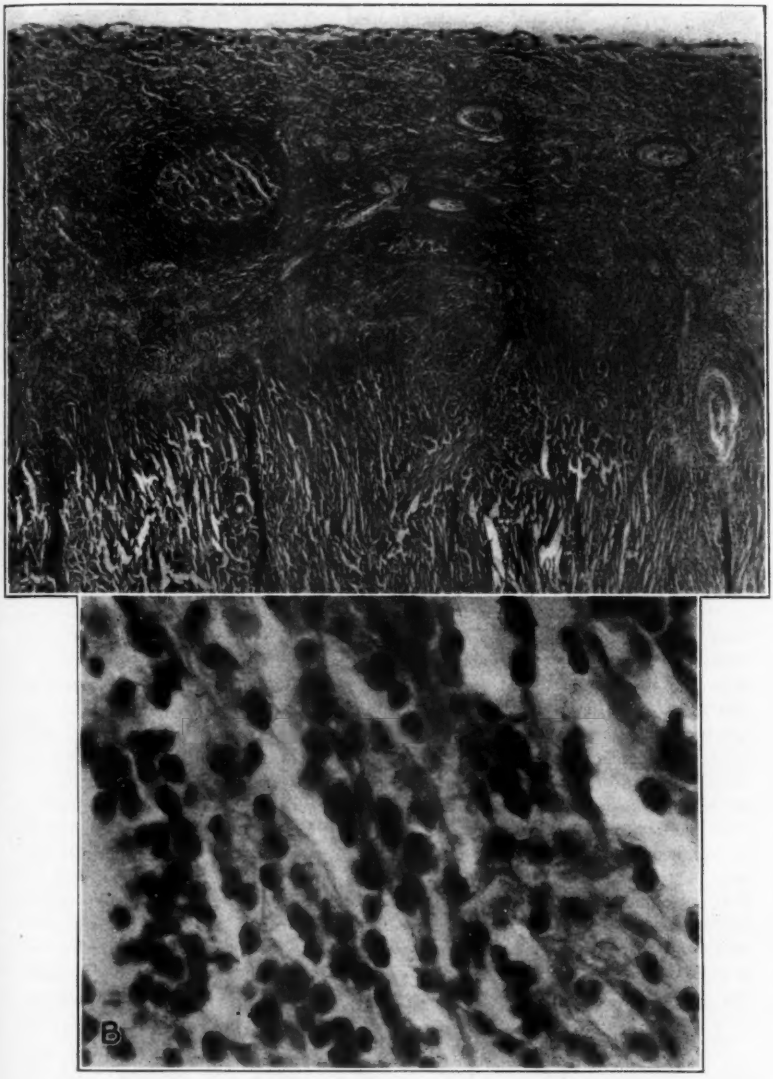
Past History.—The patient was born in the San Joaquin Valley of California. Operations included tonsillectomy and appendectomy prior to the onset of her present illness. Accidents and traumas were of minor nature. Medications prior to entry had included thyroid substance, vitamins, calcium, histamine, estrogens and sulfonamides and penicillin. There was no history of venereal disease.

Physical Examination.—The pulse rate was 106, temperature (rectal) 37 C. (98.6 F.) and blood pressure 124 systolic and 78 diastolic. The patient was a well developed middle-aged woman who held her head stiffly with little voluntary motion of the neck. The soft tissues of the neck seemed thickened, with a lack of pliability of the musculature yet without true induration. There was generalized limitation of mobility of the neck; localized tenderness was not found. Examinations of the ear, nose and throat revealed conditions within normal limits. The circumference of the head was 55.5 cm. at its greatest measurement. There was bilateral papilledema, the swelling measuring 2 D. on the right and 3 D. on the left. There were numerous hemorrhages on and near the right disk margins. Examinations of the visual fields showed enlarged blindspots bilaterally without other demonstrable defects. Visual acuity, uncorrected, was 20/50 on the right and 20/40 on the left. The rest of the results of the general and neurologic physical examinations were normal.

Laboratory Examination.—Urinalysis of a noncatheterized specimen showed a 1 plus reaction for albumin, 20 to 30 white pus cells and 2 to 5 red blood cells per high power dry field. Examination of the blood showed 4,320,000 red cells, 12.8 Gm. of hemoglobin and 6,400 white blood cells, with 61 per cent polymorphonuclears, a 56:5 ratio of filamented to nonfilamented forms, 33 per cent lymphocytes, 4 per cent eosinophils and 2 per cent basophils. The characteristics on smear were normal. Serologic tests of the blood on two examinations showed a plus-minus reading on the lowest dilution in one Kahn test. All other readings were negative. Lumbar puncture yielded fluid under an initial horizontal pressure of 300 mm. of water. The fluid was crystal clear. There were 4 lymphocytes per cubic millimeter. Total protein was 72 mg. per hundred cubic centimeters. Wassermann and Kolmer tests elicited negative reactions. The colloidal gold curve was 1112332210. Plain roentgenograms of the sinus revealed no abnormalities.

Ventriculography.—On Sept. 17, 1945, through burr holes low in the parietal area ventriculography was performed with use of local anesthesia. The dura in this region and the underlying cortex were not remarkable. The studies showed moderate symmetric dilatation of the ventricular system from the aqueduct cephalad. No displacement was seen, and filling of the aqueduct was minimal.

Operation.—On September 22, with the diagnosis of block of the fourth ventricle, possibly on the basis of a tumor of the posterior fossa, a suboccipital craniotomy was performed. A wide exposure of the occipital bone from mastoid to mastoid and down to the axis was obtained. The bone was thick and hard. When the bone was removed, including the posterior part of the foramen magnum and the arch of the atlas, the dura over the exposed area was seen to be rather shaggy



A, photomicrograph of the outer surface of the dura of the case presented. There can be seen the line of demarcation between the old fibrous, acellular dura below and the marked reaction above. A lymph follicle with its germinal center is visible together with numerous vascular channels. Hematoxylin and eosin; × 50. *B*, greater magnification of the cellular portion of the area of the dura shown above. Small round cells, eosinophils and macrophages predominate. The new delicate vascular channels can be seen along with young connective tissue. No specific changes in the blood vessels were demonstrated. Hematoxylin and eosin. × 650.

in appearance, particularly on the right side but also to some extent on the left. It resembled the appearance seen beneath an area of old osteomyelitis. When the dura was incised, it was found to be enormously altered and was 10 mm. in thickness. The stiffness was like that of sole leather. This was true over the entire right side and most of the left. Toward the left mastoid process it was less thick, measuring possibly 7 mm. The incision was extended through the foramen magnum and down to the axis. A square block of the thickened dura was excised. In the region of the foramen magnum it was fully as thick as it was superiorly. It may have been a bit thinner as one approached the upper margin of the axis. There was only moderate herniation of the cerebellar tonsils through the foramen magnum. All the dura was then excised to the limits of the bony opening in all directions. This was accomplished without event, and in only one or two places were there vessels within the dura which required coagulation. On the inner surface the dura was smooth and had more of a pale ivory color than the inner surface of normal dura. Exploration about the cerebellum and between it and the dura anteriorly, inferiorly and superiorly revealed the same smooth inner surface. The contents of the posterior fossa were normal otherwise. It was impossible to determine the anterior extent of the thickening. Fluid injected through a needle previously placed in the right lateral ventricle did not emerge from between the cerebellar tonsils. A catheter was inserted through the fourth ventricle and up the aqueduct for a distance of 8 cm. On subsequent injection, fluid flowed freely through the ventricular system. The patient's condition remained good during the procedure.

Pathologic Study.—The dura consisted chiefly of very thick, acellular, poorly vascularized collagenous tissue arranged in thick interlacing bundles and containing areas of patchy lymphocytic infiltration. The surface, which was noted to be grossly roughened and fleshy in consistency, was the site of a very marked cellular reaction with the following characteristics: (1) intense infiltration by lymphocytes, with the formation of pellicles with germinal centers; the cells of the germinal centers were of poor definition, shadowy outline and indistinct nuclear pattern; (2) occasional multinucleated cells, apparently of reticuloendothelial origin; (3) heavy, diffuse infiltration by eosinophils and plasma cell; (4) rather large numbers of large mononuclear phagocytes filled with foamy lipid material; (5) marked vascularity, and (6) proliferation of young fibrous tissue adjacent to the older fibrous tissue. The reaction bore no definite relation to blood vessels, there were no abnormalities of the vessels and no areas of necrosis or blood pigment deposition. Special stains for connective tissue supplied no additional information. Stains for bacteria and fungi gave negative results. Giemsa's stain demonstrated the lipid-filled macrophages especially well, and an acid-fast preparation stained the lipid globules faintly with carbolfuchsin. No acid-fast organisms were seen.

Course.—The patient's convalescence was slow but steady. Headache and visual disturbances were relieved. Protracted nausea and vomiting occurred on change of position. Lumbar puncture on the fifteenth postoperative day revealed fluid under an initial pressure of 138 mm. of water; there were 15 lymphocytes and 40 red blood cells per cubic millimeter. The total protein was 91 mg. per hundred cubic centimeters. Papilledema was decreasing noticeably on the patient's discharge on the twenty-sixth postoperative day.

Hospitalization Feb. 2 to 10, 1946.—The patient reentered the hospital considerably depressed by the slowness of her convalescence. She was still much below normal weight. The stiffness of the neck persisted, and she was unsteady

and had dizziness on sudden movement. A stiff left shoulder and thrombosed hemorrhoids added to her troubles. The swelling of the optic disks had subsided. The spinal fluid pressure was 170 mm. of water; the protein was 100 mg. per hundred cubic centimeters; the Wassermann and Kolmer reactions were negative, and the colloidal gold curve was 0012211000.

Recheck in May 1946.—Autopsy of the guinea pig inoculated with spinal fluid disclosed neither tuberculosis nor other infections. The patient's suboccipital area was not under tension. The cervical muscles felt less thickened. After advice and physical therapy the patient made rapid improvement, and after a few months she was able to resume her occupation.

REVIEW OF THE LITERATURE

Involvement of the dura by injury, inflammation and neoplasm is not unusual, but the type of change described, without lamination or hemorrhage, is, in our experience, novel. From the reported types, several groups, some of which overlap, may be established: (1) cases of inflammatory, although not necessarily infectious, origin; (2) those of traumatic origin; (3) those of infectious origin, specific and otherwise; (4) those of neoplastic origin, and (5) those of obscure and unknown origin. In the discussion of the first two categories the subject of traumatic subdural hematoma will receive but brief attention.

Inflammatory Origin.—In 1857 Virchow[1] reset the trend of European thought regarding the hemorrhagic manifestations of dural afflictions and stated that they were initially inflammatory, although not necessarily infectious, in origin. The hemorrhagic component of the process he considered to be secondary, although possibly the more dominant-appearing component in the later and more fully developed stages. Although dominated by Virchow's writings, the opinion subsequent to that time remained divided.

In his writings Virchow discussed the origin of blood cysts of the dura and traced the pathogenesis back to a state of chronic dural inflammation. The sac or cyst which resulted was a readily recognized hematoma.[2] The condition was probably first described in France about 1835 under the name of serous cysts of the arachnoid.[3] Virchow collected his cases among patients with mental disease and with infectious conditions. He suggested the possibility that hemorrhagic diatheses as well as inflammatory states might give rise to hematomas of the dura. He described the pathogenesis as follows: In the beginning

1. Virchow, R.: Das Hämatom der Dura mater, Verhandl. d. phys. med. Gesellsch. **7**:134, 1857.

2. Haranghy, L.: Zur Kasuistik der durch Pachymeningitis hemorrhagica entstandenen Blutzysten, Centralbl. f. allg. Path. u. path. Anat. **53**:65-69 (Nov. 20) 1931.

3. Rosenberg, O.: Die Pachymeningitis hemorrhagica im Kindesalter, Berlin klin. Wchnschr. **50**:2272-2274, 1913.

there is slight bleeding, and a layer of fibrin forms with small spots of blood similar to capillary bleeding. Later the fibrin becomes thicker and can be seen macroscopically. At the site of the blood spots there is deposition of pigment, and the older the bleeding the thicker these spots become. The process repeats itself, layering one pseudomembrane on top of the other. Virchow expressed the belief that the process could originate on the inside, outside or both sides of the dura and that the external form was like a periostitis. As many as twenty layers might form, which might be separated one from the other and if thick enough might fuse with the arachnoid. More vessels were derived from the arachnoid; they were greater in number and size than normal and had many anastomoses. The bleeding was heavier, and the blood of the hematoma from these vessels was lost into the sac which had formed between the pseudomembranes. This sac was closed to all surfaces.

It was argued that the membrane was present before the bleeding—i. e., that the membrane could be present with only very small extravasations of blood—that the extravasations were always fresher than the membranes and that the sac contained normal as well as destroyed blood, as does an aneurysmal sac. At times there was no inflammatory reaction in the dura itself, for if the condition were old then the inflammatory reaction was seen in the pseudomembranes which had more vessels; when the membranes were removed the dura was normal. The dural reaction in his example of a serous fluid collection was the same as that when blood was present between the membranes.

Cornil, Charcot and Vulpian, cited by Marie, Roussy and Laroche [4] supported the inflammatory theory of Virchow, as did Melnikow-Raswedenkow, cited by Fahr.[5] Tissot,[6] in his review of opinion both prior to and immediately following Virchow, included trauma as a factor of occasional etiologic importance but considered hemorrhagic pachymeningitis in most cases to be due to a chronic inflammatory state involving the inner aspect of the cranial dura.

Blackburn [7] championed the theory of Virchow and expressed the belief that the origin of the hematoma was primarily on an inflammatory basis. Of the 8 cases that he reviewed, the clots in those without

4. Marie, P.; Roussy, G., and Laroche, G.: Les Pachyméningites hémorrhagiques (étude anatomique, histologique et expérimentale), Tr. Internat. Cong. Med. London (Neuropath.) **2**:173-182, 1913.

5. Fahr, T.: Histologische Beiträge zur Frage der Pachymeningitis, Centralbl. f. allg. Path. u. path. Anat. **23**:977-981, 1912.

6. Tissot, F.: La pachyméningite cérébrale hypertrophique, Progr. méd., Paris **27**:421-431, 1911.

7. Blackburn, I. W.: Pachymeningitis Interna, J. Nerv. & Ment. Dis. **38**: 467-476 (Aug.) 1911.

a history of trauma appeared older and more nearly healed. He stated the belief that the features which were usually considered as differentiating the traumatic form from the nontraumatic form, such as the development of endothelium in the latter, were rather differences in degree of organization than differences in type. This author concluded that the two conditions were identical clinically and pathologically.

Boeckmann [8] also expressed the opinion that trauma was not a causative factor in the formation of the membranes and blood sac, and he presented the evidence of the lack of such formations postoperatively after craniotomy. Goralewski [9] likewise argued from 2 cases that there was no connection between trauma and hemorrhagic pachymeningitis. Similar expressions were made by others.[10]

The picture of nontraumatic pachymeningitis hemorrhagica interna was given by Barratt.[11] He stated the opinion that the earliest changes recognizable were swelling and proliferation of the endothelial cells on the inner surface of the dura. Dilatation of the capillaries of the inner layer of this membrane followed, and exudate of fibrin formed a layer on the free surface of the dura. Free cells together with fibroblasts and new capillaries appeared in the exudate, which ultimately was replaced by fibrous tissue. Hemorrhage was common, but not invariable, and it was not a necessary prelude to the formation of the subdural membrane. In the last respect, Barratt certainly supported Virchow's thesis. He stated further that the process of intravascular clotting, as he described it, was the immediate factor leading to dilatation of vessels and extravasation of blood. The separation of fibrin was not the result of an acute irritative process, such as occurred in pneumonia, and the cells which made their appearance were mononuclear cells, indicating a more chronic process. Wohlwill [12] indicated that he thought the process showed no evidence of growth of endothelium—i. e., was not a proliferative process but rather the organization of an already existent exudate or hematoma. Blackburn [7] stated the belief that the essential feature of pathogenesis was the primary formation of a fibrous exudation on the inner surface of the dura as the result of some irritation and that at the same time the dural surface was denuded of endo-

8. Boeckmann, E.: Ein Beitrag zur Aetiologie der Pachymeningitis interna haemorrhagica, Virchows Arch. f. Path. Anat. **214**:380-388, 1913.

9. Goralewski, G.: Tumorähnliche Bilder bei Pachymeningitis haemorrhagica, Med. Welt. **9**:1179-1181 (Aug. 16) 1935.

10. Schwartz, A. B.: The Etiology of Pachymeningitis Hemorrhagica Interna in Infants, Am. J. Dis. Child. **11**:23-32 (Jan.) 1916. Barré, J. A., and Masson, J.: Hématome non traumatique de la dura-mère, Encéphale **28**:81-102 (Feb.) 1933.

11. Barratt, J. O. W.: On Pachymeningitis Hemorrhagica Interna, Brain (pt. 2) **15**:181-225, 1902.

12. Wohlwill, F.: Ueber Pachymeningitis hemorrhagica interna, Virchows Arch. f. path. Anat. **214**:388-408, 1913.

thelium, permitting emigration of leukocytes and proliferating connective tissue cells into the meshes of the fibrinous layer. He expressed the further opinion that at first this new membrane showed no hemorrhage or even pigmentation, but the thin-walled vessels which grew into it from the dura were easily ruptured, resulting in hemorrhage within the membrane or between it and the dura. Though hemorrhage was almost the rule, he felt that it was by no means always a prominent feature. Rössle [13] described a chronic form of pachymeningitis hemorrhagica which was an exudative form and quite avascular. He felt that it formed because of inflammation and that the lamination of psuedomembranes was explained by transudation through the neomembrane of blood elements with solidification followed by further transudation and formation of another layer. According to his description, leukocytes were seen rarely, as were plasma cells, and in some cases there were lymphocytes. Some larger, unnamed cells were also present, and there were cellular nodules deep in the membrane consisting of lymphatic channels which were obstructed by epithelial cells. The old dura, however, was unchanged.

Jores and Laurent [14] in 1901 described an idiopathic form of hemorrhagic pachymeningitis. The type was characterized by the particular proliferation of the subendothelial capillary layer of the dura with formation of a very vascular membrane. As cited by Marie and co-workers,[4] Baillarger and Buss, earlier, and van Vleuten, subsequently, favored the occurrence of primary hemorrhage with organization, a noninflammatory form. Fahr [5] in 1912 presented 2 cases to which he applied the term "pachymeningitis vasculosa," referring to a primary capillary proliferation with blood diapedesis, deposition of pigment and fibrosis with the formation of a fine membrane. He stated the belief that this type could occur in chronic form as a clearcut entity without the occurrence of a precursory fibrinous process—i. e., without an inflammatory process. He felt that this type with progressive capillary and endothelial proliferation might occur as a pure form or exist in combination with the serofibrinous inflammatory reaction of Virchow. Although Melnikow-Raswedenkow, cited by Fahr,[5] refuted this noninflammatory form, Rössle [13] supported it and reported a case of vascular pachymeningitis which did not arise from a fibrinous form but seemingly arose as an independent process. Rosenberg [3] reviewed 38 cases in children in which he felt that the pathologic change was a matter of a primary capillary proliferation together with proliferation of the connective tissue

13. Rössle, R.: Zur Systematik der Pachymeningitiden, Centralbl. f. allg. Path. u. path. Anat. **20**:1043, 1909; Gummöse Pachy-leptomeningitis, München. med. Wchnschr. **63**:1330, 1916.

14. Jores, L., and Laurent: Zur Histologie und Histogenese der Pachymeningitis hemorrhagica interna, Beitr. z. path. Anat. u. z. allg. Path. **29**:486, 1901.

stroma. He hinted, however, that acute infectious diseases might have an obscure role in the pathogenesis, the proliferation being of inflammatory origin.

Brunner [15] considered internal hemorrhagic pachymeningitis as due to a primary proliferation of the submesothelial tissue, probably following a lesion of the dural mesothelium. The proliferation became associated with a fibrinous exudate and hemorrhages. Later blood organization led to membrane formation and deposition on the inner aspect of the dura. This writer was in many respects in accord with Barratt [11] and Jores and Laurent.[14]

Putnam and Putnam [16] stated the belief that the idiopathic or vascular or nontraumatic pachymeningitis membrane could be found with or without hemorrhage. The membrane was composed of a network of large capillary-like vessels. The reactive type of membrane following trauma, they felt, always followed hemorrhage into the subdural space. This membrane was characterized by the presence of spaces, at times filled with blood, which were much larger than those in the nontraumatic form. These anastomosed with one another and with apparently normal capillaries seen elsewhere in the membrane.

Marie, Roussy and Laroche [4] described three forms of hemorrhagic pachymeningitis based on the study of 49 cases. The arborescent form was characterized by an abundance of newly formed vascular channels making up a neomembrane; this was a veritable angiomatous state with few hemorrhages. The hemorrhagic form was a thin, exudative, petechial type or a diffuse or encysted form. Their last form was an ochrous type (ochre pigment) with large deposits of blood pigment. Mixed forms occurred, but the essential characteristic was the new vascular formation. These authors felt that the inflammatory theory explained most cases but that primary hemorrhages might occur.

It will be remembered that these two forms discussed were regarded as nontraumatic in origin. From our survey it is not possible to differentiate between these so-called primary, idiopathic vascular forms and the inflammatory form of Virchow. As Blackburn [7] mentioned, the proliferative endothelial changes were used to distinguish the nontraumatic from the traumatic forms, but these changes probably could not be considered characteristic of a distinct pathologic type. Such is probably true in the foregoing discussion.

Traumatic Origin.—The traumatic basis for hemorrhagic and hematomatous dural formations is firmly established. The pathology of

15. Brunner, H.: Intracranial Complications of Ear, Nose and Throat Infections, Chicago, The Year Book Publishers, 1946, p. 142.

16. Putnam, T. J., and Putnam, I. K.: The Experimental Study of Pachymeningitis Hemorrhagica, J. Nerv. & Ment. Dis. **65**:260-272 (March) 1927.

subdural hematoma has been presented quite thoroughly by Blackburn,[7] Cabot and Cabot,[17] Griswold and Jelsma [18] and Putnam and Cushing [19] and will not be considered here. When applied to traumatic subdural hematomas the term pachymeningitis is misleading, but numerous examples of this terminology are encountered, including the cases of Totherick,[20] Madigan,[21] Rosenthal [22] and Jaeger.[23] Other cases appear under the heading of subdural hematoma in which inflammation undoubtedly plays a part. In a certain percentage of these dural formations, though no history of trauma is obtained, a pathologic picture is present which is identical with that of the traumatic cases. Certain authors (earlier writers principally) have expressed the opinion that none of the cases occur on a traumatic basis. Some have felt that all have such a basis, and a few have written that a combination of trauma and other factors is necessary for the production of this picture. It would appear further that the earlier writers also accepted the occurrence of a primary hemorrhagic pachymeningitis of neither traumatic nor inflammatory origin.

That trauma might be a factor in the causation of these lesions was admitted by Jores and Laurent.[14] They agreed that a genuine hemorrhagic lesion could occur from trauma but stated that the stratified membrane so formed on the dura could not be considered the same as that of the primary proliferative process. Rosenberg [8] distinguished between the hemorrhagic membranes occurring after birth trauma and the inflammatory types. He recognized a form following hemorrhagic diatheses as approximating the post-traumatic picture. Middlemass and Robertson [24] recognized traumatic and infective dural reaction with

17. Cabot, R. C., and Cabot, H.: Cabot Case, Boston M. & S. J. **194**:592-596 (April 1) 1926.

18. Griswold, R. A., and Jelsma, F.: Relationship of Chronic Subdural Hematoma and Pachymeningitis Hemorrhagica Interna: Report of Eight Cases, with Report of Finding Bile Pigment in Hematoma, Arch. Surg. **15**: 45-56 (July) 1927.

19. Putnam, T. J., and Cushing, H.: Chronic Subdural Hematoma, Arch. Surg. **11**:329-393 (Sept.) 1925.

20. Totherick: Case of Pachymeningitis: Necropsy, Lancet **2**:106 (July 19) 1884.

21. Madigan, P. S.: Encephalography in Cerebral Surgery and Report of Case of Pachymeningitis Interna, with Cyst Formation, Successfully Removed, Mil. Surgeon **66**:390-397 (March) 1930.

22. Rosenthal, R.: Pachymeningitis Hemorrhagica Interna: Report of Case with Recovery, Minnesota Med. **14**:547-550 (June) 1931.

23. Jaeger, J. R.: Pachymeningitis Hemorrhagica Interna, Colorado Med. **27**:343-346 (Sept.) 1930.

24. Middlemass, J., and Robertson, W. F.: Morbid Condition of the Dura Mater, Edinburgh M. J. **40**:704-729 (Feb. 18) 1895.

hemorrhage into the subdural space. They also described a true hemorrhagic pachymeningitis of the insane of which we will speak again subsequently.

The group of authors which admits that a certain percentage of cases is on a traumatic basis includes Wohlwill.[12] He distinguished between the traumatic and the nontraumatic entities. He concluded that a vascular membrane and the presence of old pigment permitted the diagnosis of a truly inflammatory process. He stated the belief that the majority of cases were on the inflammatory basis but that a division should be made between a primary vascular form, a fibrinous or exudative form and a purely serous form. Von Sarbó [25] distinguished a traumatic form from others, and Rössle [13] had previously described one form due to trauma and one to a primarily vascular process of the type of Jores and Laurent.[14] Of the 3 cases of Hohlbaum,[26] 2 were considered idiopathic, whereas the third was of traumatic origin. Kowitz,[27] after reviewing 5,998 autopsies on infants, concluded that a distinction ought to be made between idiopathic and traumatic subdural bleeding. His example of the nontraumatic form was an external pachymeningitis in which the dura had grown to the bone. The traumatic origin of infantile subdural bleeding was amply borne out by Courville's 226 cases of tears of the falx cerebri and tentorium cerebelli.[28]

According to van der Horst,[29] the structure of the membrane was the distinguishing feature between the two forms. In the nontraumatic cases he found a very cellular connective tissue with irregular vacuolations filled with blood and thickening of the dura. In the traumatic forms the dura was normal and an organized thrombus was separated from the dura by fibrous tissue. It will be recalled that Virchow felt that if the condition (inflammation) were old then the dura beneath the pseudomembranes was normal. Courville,[28] in his analysis of 30,000 autopsies, discovered 371 examples of hemorrhagic effusion into the subdural space, of which 226 were in infants. Of the remaining effusions, 51 occurred in persons past middle age, and in these patients degenerative vascular disease was presumed to be the underlying etiologic factor. In 34 cases the effusion was considered due to trauma.

25. von Sarbó, A.: Internal Hemorrhagic Pachymeningitis, Deutsche Ztschr. f. Nervenh. **92**:216-239, 1926.

26. Hohlbaum, J.: Zur Aetiologie und Therapie der Pachymeningitis hemorrhagica interna, Arch. f. klin. Chir. **164**:181-195, 1931.

27. Kowitz, H. L.: Intrakranielle Blutungen und Pachymeningitis hemorrhagica chronica interna, Virchows Arch. f. path. Anat. **215**:233-246, 1914.

28. Courville, C. B.: Pathology of the Central Nervous System, ed. 2, Mountain View, California, Pacific Press Publishing Association, 1945, pp. 100, 101, 158, 193-195 and 212.

29. van der Horst, L.: Dura-hämatom oder Pachymeningitis hemorrhagica interna, Deutsche Ztschr. f. Nervenh. **125**:117-128, 1932.

The remaining cases were those with varying causative factors, and in this group 22 cases were found for which no specific cause could be discovered. It was thought that trauma could well have been the responsible factor. In the nontraumatic cases the evidence of recurrent hemorrhage with lamination of the neomembrane was not commonly found. This lamination has been considered a distinguishing feature of nontraumatic cases.

The evidence and studies of Putnam and Cushing,[19] Griswold and Jelsma [18] and Holmes [30] support the present generally accepted theory that most subdural hematomas of clinical significance are of traumatic origin. Certain exceptions and variations must undoubtedly be admitted. Volante,[31] for example, expressed the opinion that the primary cause of the pachymeningitis was minute traumatic hemorrhage, related to abnormal fragility of the capillaries from various toxic or inflammatory influences and to local intracapillary stasis and an increase in intraluminal pressure. Internal hemorrhagic pachymeningitis as related to infancy has been discussed by many others, including Burhans and Gerstenberger,[32] Cathala and Wolff,[33] Debré and Semelaigne,[34] Feer,[35] Finkelstein,[36] Glaser,[37] Goppert,[38] Heubner,[39] Hunt,[40] Kowitz,[27] Rosenberg,[3] Rosenthal,[22] Schwartz [10] and Sutherland.[41]

30. Holmes, W. H.: Cases Illustrating Symptomatology of Brain-Stem Lesions and of Chronic Subdural Hemorrhage, M. Clin. North America **9**:1541-1562 (May) 1926; Chronic Subdural Hemorrhage: Subdural Hemorrhagic Cyst; Traumatic Pachymeningitis Hemorrhagica Interna; Compression Tardive with Report of Cases, Arch. Neurol. & Psychiat. **20**:162-170 (July) 1928.

31. Volante, F.: Sulla patogenesi della pachymeningite hemorrhagica interna, Gior. d. r. Accad. di med. di Torino **96**:185-190 (July-Sept.) 1933.

32. Burhans, C. W., and Gerstenberger, H. J.: Internal Hemorrhagic Pachymeningitis in Infancy, J. A. M. A. **80**:604-609 (March 3) 1923.

33. Cathala, J., and Wolff: Hémorragie méningée par pachyméningite hémorragique chez le nourrisson, Bull. Soc. de Pédiat. de Paris **24**:321-326 (Oct.-Dec.) 1926.

34. Debré, R., and Semelaigne, G.: Hemorrhagic Pachymeningitis in Infants, Presse méd. **34**:337-339 (March 17) 1926.

35. Feer, E.: Die Pachymeningitis hemorrhagica interna, Cor. Bl. f. schweiz. Aerzte. **45**:598, 1915.

36. Finkelstein, O.: Die Pachymeningitis hæmorrhagica interna im Kindesalter, cited by Rosenberg.[3]

37. Glaser, H.: Ein Beitrag zur Frage der Pachymeningitis haemorrhagica interna, Arch. f. Kinderh. **91**:102-105 (July 25) 1930.

38. Goppert, F.: Drie Fälle von Pachymeningitis haemorrhagica mit Hydrocephalus externus, Jahrb. f. Kinderh. **61**:51-63, 1905.

39. Heubner, O.: Pachymeningitis haemorrhagica bei hereditärer Syphilis, Virchows Arch. f. path. Anat. **84**:267-274, 1881.

40. Hunt, F. C.: Internal Hemorrhagic Pachymeningitis in Young Children: Report of Six Cases, Am. J. Dis. Child. **39**:84 (Jan.) 1930.

41. Sutherland, G. A.: On Haematoma of the Dura Mater Associated with Scurvy in Children, Brain **17**:27-36, 1894.

We have considered two groups, the inflammatory cases and the traumatic cases. They are not too sharply divided. It seems reasonable that many of the cases even without any history of trauma are to be explained on a traumatic basis.

Other theories have been proposed for those cases which are not felt to have a traumatic origin. It must be emphasized, as mentioned previously, that the same pathologic picture may exist in many cases the origins of which seem foreign to one another, and different stages of the same pathologic process may produce pictures and entities whose differences are more apparent than real.

Virchow studied his cases from among patients with mental disease and those with inflammatory conditions. Huguenin [42] cited chronic alcoholism as a possible or probable cause of the hemorrhagic membranes. Gordon [43] claimed insanity and old age to be important causes. Fisk [44] suggested a combination of old age and alcoholism; however, his case was one of obscure cause, but the membrane answered the description of a traumatic hematoma. The role of hemorrhagic diathesis in causation has been covered by several writers (Fried,[45] Gordon,[43] Henschen,[46] Rosenberg [3] and Virchow [1]). Goralewski [9] considered the pathologic state only a syndrome secondary to many chronic and acute diseases as well as alcoholism, dementia senilis, blood diseases and other conditions. Middlemass and Robertson [24] proposed a widespread morbid process in the form of fatty degenerative changes in the substance of the dura of insane patients who had subdural membrane formation. They felt that trauma and infection were no commoner as causative factors in insane persons than in mentally sound persons, but they thought that the fatty degenerative changes could cause or predispose to hemorrhage. These authors also described physical factors and a theory of "dry cupping" of the dura which would contribute to the initiation of hemorrhage in the presence of degenerative processes. Tissot [6] listed as of primary importance alcoholism, syphilis and infectious diseases associated with cachexia. From his 3 cases, La Fora [47]

42. Huguenin, G.: Pachymeningitis Interna, in Ziemssen, H. W.: Cyclopedia of the Practice of Medicine, New York, William Wood, 1877, vol. 12, pp. 375-426.

43. Gordon, A.: Internal Pachymeningitis in Young Children, New York M. J. **99**:720-723 (April 11) 1914.

44. Fisk, G. H.: Case of Pachymeningitis Hemorrhagica Interna, Canad. M. A. J. **29**:412-415 (Oct.) 1933.

45. Fried, H.: Pachymeningitis Hemorrhagica Interna, M. J. & Rec. **119**: 149-151 (Feb. 6) 1924.

46. Henschen, C.: Zur Pathologie, Diagnostik und Therapie der "blutenden Dura" (Pachymeningiosis et Pachymeningitis hemorrhagica interna), Schweiz. med. Wchnschr. **11**:599-609 (June 28) 1930.

47. La Fora, G. R.: Ueber umschriebene bindegewebige Verdickungen an der inneren Fläche der Dura, Virchows Arch. f. path. Anat. **210**:48-50, 1912.

was unable to state the origin or pathogenesis of the hemorrhagic process. He did not favor a "vascular origin" but felt that the bleeding occurred through some type of reactive process of the connective tissue about the capillaries and that the blood was resorbed, leaving the pigment-filled cells behind. Rosenberg [3] listed acute infectious diseases among possible etiologic factors, and Lucke [48] also considered the role of certain such diseases but was not sure whether the fibrinous exudate on the inner surface of the dura in such cases could give rise to the chronic type of hemorrhagic pachymeningitis through organization of the layer. Putnam and Putnam [16] recognized the nontraumatic, idiopathic form of pachymeningitis and felt it was seen in persons with chronic alcoholism and insane persons. They also felt that hemorrhagic diseases such as pernicious anemia, leukemia and purpura were sometimes associated with hematomatous pachymeningitis.

Holmes [30] argued that the reason the pathologic state was found in such frequency among alcoholic addicts and the insane was because they were just the ones to receive the minimal trauma necessary for the initiation of the subdural bleeding. Certainly the anamnesis from such cases was unreliable. We feel that those cases attributed to sunstroke and those which answer the clinical criteria of spontaneous subarachnoid hemorrhage (Dunn,[49] Fried [45] and Sonnenfeld [50]) should not be included.

It should be noted that experimental investigation has shed little light on the genesis of pachymeningitis hemorrhagica. In 1913 Marie and co-workers [4] attempted to produce experimentally a hemorrhagic state by the injection of plain blood and blood incubated with staphylococci beneath the dura of animals. They concluded from a small series of experiments that some irritant, either bacterial or chemical, was necessary to produce the lesion in question. Boeckmann [8] observed 57 cases of operative bleeding from craniotomies which came to autopsy. There were no cases of hemorrhagic membranous pachymeningitis, and therefore he felt that trauma was not the important cause. The earlier culture work of Barratt [11] demonstrated the freedom of the subdural membrane from bacterial organisms. Putnam and Putnam [16] in 1927 cited the experimental work of Sperling in 1872 and van Vleuten in 1898 among others. By subdural injections of blood into animals these workers produced experimental hematomas which showed some microscopic differences from those seen in human patients. The primary difference, however, was their lack of progression as a pathologic lesion

48. Lucke, B.: Acute Infectious Internal Hemorrhagic Pachymeningitis, Proc. Path. Soc., Philadelphia **22**:74, 1919-1920.

49. Dunn, A. D.: Pachymeningitis Hemorrhagica Interna, Am. J. M. Sc. **163**:819-825 (June) 1922.

50. Sonnenfeld, A.: Zur Aetiologie der Pachymeningitis hæmorrhagica interna, med. Klin. **22**:656-657 (April 23) 1926.

of note. The postoperative cases studied by these men likewise did not show the progressive hemorrhagic changes seen in pachymeningitis.

It would appear, then, that hemorrhagic manifestations may involve the dura with greater or less amounts of change from the normal state and almost universally with a proliferative or laminative process with the construction of one or many pseudomembranes. This membrane or series of membranes has varying degrees of attachment to the dura. It is accepted that while the majority of cases occur primarily on a traumatic basis, yet other primary etiologic factors must be acknowledged. It may not be possible pathologically to distinguish between the two. We cannot, from a perusal of the arguments in the literature, conclude that there is no possibility of a "primary," or idiopathic, form of hemorrhagic pachymeningitis. We suggest, however, that this group probably will find etiologic classification among the presently recognized groups as knowledge widens.

Infectious Origin.—In the third large class, the infectious group, we will not consider the leptomeningitides, the subdural, intradural and epidural abscesses or the empyemas but will consider only those conditions which simulate the pathologic picture heretofore described and a few special ones in addition.

In an excellent outline and review, Henschen [46] listed under hemorrhagic pachymeningitis the inflammatory reaction of the meninges due to neighboring infection, such as otitis media. There would be, in truth, a sterile inflammatory reaction of the pachymeninx. Brunner [15] observed several cases of hemorrhagic pachymeningitis associated with disease of the ears but felt that the findings were coincidental and that the otogenous origin of internal hemorrhagic pachymeningitis was not proved. Courville and Blomquist [51] described the reaction of the dura in such cases. They felt that the dura would react to neighborhood external infection as did other tissue of primarily connective tissue composition with congestion, exudation and formation of granulation tissue. When the inflammatory reaction was unaccompanied with any gross accumulation of purulent exudate, the lesion was properly designated as pachymeningitis externa or interna as the case might be. Similar cases have been included in the discussion of the inflammatory but not infectious group just completed and have been reported by others (Clein,[52] de Jong,[53] Goralewski,[9] Gordon,[43] Krepuska,[54]

51. Courville, C. B., and Blomquist, O. A.: Traumatic Pachymeningitis Interna and Subdural Abscess, Arch. Surg. **42**:890-908 (May) 1941.

52. Clein, N. W.: Pachymeningitis Hemorrhagica Interna, Northwest Med. **29**:153-154 (April) 1930.

53. de Jong, R.: Hemorrhagic Meningitis Secondary to Anthrax Bacillus, Nederl. tijdschr. v. geneesk. **2**:484 (Aug. 11) 1917.

54. Krepuska, S.: Die Pachymeningitis hæmorrhagica interna vom otologischen Gesichtspunkte, Ztschr. f. Hals-, Nasen-, u. Ohrenh. **17**:419-437 (Feb. 22) 1927.

Swift [55] and Volante [31]). It is difficult to understand the reasoning of Kasenmeyer,[56] who presented a case of subdural hematoma followed five years later by leptomeningitis. He felt the area of lowered resistance at the site of the fibrous pachymeningitis permitted the infectious process to be superimposed.

Henschen [46] separated from the noninfectious group the primarily bacterial hemorrhagic pachymeningitis accompanying other infectious systemic disease. Cultural proof is necessary to make this distinction, for in cases of tuberculosis and syphilis the gross appearance of the membranes may simulate that of purulent exudate (Holt,[57] Wiersma [58] and Wohlwill [12]). The 2 cases of Horne,[59] showing intradural abscess with further extension of a purulent process, illustrated the possibility of marked dural participation in purulent disease processes from adjacent areas. Epidural and subdural abscess have been discussed elsewhere. Brunner,[15] speaking of these conditions, stated that a serous type of pachymeningitis probably did form but could scarcely be proved because of spontaneous cure. This author felt that if a serous exudate or only a small amount of pus were produced then spontaneous cure was likely, with resulting adhesions between the dura and arachnoid. Courville [28] also described mild inflammatory reactions of the internal dural surface as accumulations of fibrin or granulation tissue just internal to a primary extradural purulent lesion. He expressed the opinion that this reaction was not of clinical importance or significance. Cases of healed subdural abscess are almost unheard of, but in old cases some evidence of invasion of the dura is sometimes found. The exudative granulation layer on the inner dural surface is bound to the dura by vascular sprouts, and as organization progresses the sharp delineation between the neomembrane and the old dura disappears (Courville [60]). Such a case conceivably could present difficulty in classification as being primarily an infectious process when cultural proof would be lacking in late or cured stages. Ertl [61] also described the pathogenesis of this inflamma-

55. Swift, G. W.: Hemorrhagic Pachymeningitis, Northwest Med. **24**:232-235 (May) 1925.

56. Kasenmeyer, E.: Ueber posttraumatische Pachymeningitis, Deutsche med. Wchnschr. **38**:2020, 1912.

57. Holt, L. E.: Chronic Pachymeningitis: Acute Leptomeningitis, Proc. New York Path. Soc. 1887, pp. 77-79.

58. Wiersma, D.: Remarkable Case of Pachymeningitis Hypertrophica Presenting Spinal Block and Froin's Syndrome, J. Neurol. & Psychopath. **8**:209-222 (Jan.) 1928.

59. Horne, J.: Formation of Circumscribed Abscess at Site of Saccus Endolymphaticus, J. Laryng. & Otol. **42**:818-823 (Dec.) 1927.

60. Courville, C. B.: Subdural Empyema, Arch. Otolaryng. **39**:211-230 (March) 1944.

61. Ertl, E. E.: Ein Beitrag zur pathologischen Anatomie, Diagnostik und Therapie der otogenen Pachymeningitis interna infectiosa, Arch. f. Ohren-, Nasen-, u. Kehlkopfh. **149**:119-155, 1941.

tory process which might lead to a binding together of the dura and leptomeninges in an adhesive nonpurulent state.

Syphilis and tuberculosis produce dural changes of note. It is convenient to consider the changes seen in the cranial dura separately from those in the spinal dura. Heubner [62] stated that syphilitic new growths might affect the dura alone. The change was a fibrous modification of the cellular neoplasm, or more frequently, the dry, yellowish tumor or gumma usually seen in the large duplications of the dura. These small tumors, the size of beans, generally ran into the surface of the brain, and the cortex would be changed into a gummatous mass. The new growth might lose completely the character of a circumscribed tumor and take on that of a diffuse infiltration, actually a gummatous meningitis. All the membranes of one hemisphere or of both would then grow into a thick, brawny mass. The yellow tumor masses were surrounded by thickened membranes with the interstices of the connective tissue infiltrated with rows of round cells and with changes in the overlying bone (Guldberg,[63] Nonne [64] and Thompson [65]).

Nonne [64] stated that the gummatous variety of meningitis was almost without exception combined with a fibrous hyperplastic meningitis. The dura was often thickened to several times the normal thickness. It was usually adherent to the arachnoid and pia. The connective tissue was old and poor in cells. Between the fasciculi were irregularly placed, small-celled proliferations which always followed the blood vessels and sprang from them. As far as the simple meningitis was concerned, Heubner and Nonne felt that a gummatous process might have existed primarily and then subsided, leaving the hyperplastic meningeal change. Later examination of the membranes would then present nothing specific in character to identify the process. The report of gummatous pachymeningitis by Mott [65a] was well illustrated. The fibrous bundles of the dura were swollen and separated by an unequally distributed infiltration of lymphocytes and plasma cells. Nodular aggregations of these cells in some areas had undergone necrosis, and a periarteritis, and in places a marked endarteritis, were characteristic. In only a few areas was there any symphysis between the dura and

62. Heubner, O.: Syphilis of the Brain and Nervous System, in Ziemssen, H. W.: Cyclopedia of the Practice of Medicine, New York, William Wood, 1877, vol. 12, pp. 294-371.

63. Guldberg, G.: Pachymeningitis hemorrhagica interna bei Lues congenita, Arch. f. Dermat. u. Syph. **157**:409-418, 1929.

64. Nonne, M.: Syphilis and the Nervous System (translated by Ball), Philadelphia, J. B. Lippincott, 1913.

65. Thompson, A. O.: On Pachymeningitis Chronica Externa with Reference to Its Effect on the Skull, J. Path. & Bact. **2**:75-79, 1894.

65a. Mott, F. W.: A Case of Localized Syphilitic Pachymeningitis Cerebri, Arch. Neurol. & Psychiat. **4**:63-69, 1909.

leptomeninges, but when this occurred the center of the reaction was in the pia. A slight degree of osteitis was present. Smith's [66] and Seguin's [67] exhibit of syphilitic pachymeningitis showed the thickened dura over one hemisphere to be adherent to the brain, which showed softening at the points of contact of the meninges. Rössle's case [13] of a gummatous caseating lesion of the dura of one hemisphere in a 13 year old child contained no detailed description. The case of supposed pachymeningitis reported by Wessels,[68] which showed a thickened dura adherent to the bone together with a positive serologic reaction of the blood, does not stand careful analysis.

The case of cerebral pachymeningitis described by Homen [69] in 1898 was an example of diffuse dural infiltrations and thickening on a syphilitic basis. It is in these more diffuse cases that we are most interested. Hassin [70] in 1918 reviewed the literature and presented 2 cases of spontaneous pachymeningitis with enormous dural thickening. He mentioned the hyperplastic fibrous meningitis previously described and the "sclerogummatous meningitis" of Sezary.[71] He reached the conclusion that the sole cause was syphilis and that there was a simultaneous involvement of all three membranes as well as the brain substance itself. He placed the primary site of origin in the pial vessels. In 1940 the same author with Zeitlin [72] reported a case of syphilitic cerebral hypertrophic pachymeningitis with immense infiltration by plasma cells, especially of the dural interstitial spaces. There was a panarteritis and general hyperplasia of the vessel walls. There was a lack of the "cheesy" degeneration seen with tuberculous pachymeningitis. In this case the dura alone was affected.

Courville [28] described a thickening of the dura by granulation tissue as often accompanying syphilitic osteitis of the skull. This he termed "syphilitic pachymeningitis frontalis" and stated that it usually affected

66. Smith, A. H.: Syphilitic and Simple Pachymeningitis, M. Rec. **11**:146 (Feb. 29) 1876.

67. Seguin, E. C.: Syphilitic and Simple Pachymeningitis, M. Rec. **11**:163 (Feb. 29) 1876.

68. Wessels, A. B.: Pathogenesis of Pachymeningitis Due to Nasal Operations, California State J. Med. **17**:383, 1919.

69. Homen, E. A.: Zur Kenntniss der grossen meningealen und Gehirngummata, so wie der Rückenmarksyphilis, Arch. f. Dermat. u. Syph. **46**:55-78, 1898.

70. Hassin, G. B.: Histogenesis of Cerebral Hypertrophic Pachymeningitis, Am. J. Syph. **2**:715-726 (Oct.) 1918; Circumscribed Suppurative (Nontuberculous) Peripachymeningitis, Arch. Neurol. & Psychiat. **20**:110-129 (July) 1928.

71. Sezary, A.: Classification des méningites syphilitiques, J. méd. franç **7**:201-206, 1913.

72. Hassin, G. B., and Zeitlin, H.: Syphilitic Cerebral Hypertrophic Pachymeningitis: Clinicopathologic Studies in Case, Arch. Neurol. & Psychiat. **43**: 362-371 (Feb.) 1940.

the external surface but at times both layers of the dura. It was considered a reactive manifestation to the disease of the cranial vault. He also recorded 2 cases of dural gummas; these were, like other gummas, readily recognized by their characteristics.

The role of tuberculosis in the genesis of pachymeningitis was cited early as a possibility and has subsequently been proved (Brunner,[15] Courville,[28] Fried,[45] Gordon,[43] Grosz,[73] Hassin and Zeitlin,[72] Henschen,[46] Holt,[57] Miller,[74] Thompson [65] and Tooth [75]). Brunner [15] recognized two types: that commonly caused by tuberculous meningitis and marked by small tuberculous nodulations on the inside of the dura, and the external type, usually arising from an infection outside the dura. Such areas of infection he listed as tuberculous otitis media, osteomyelitis and sinusitis. This type showed diffuse or nodular infiltrations, ulcerations and granulations, usually on the outside of the dura but rarely extending to the internal dural layer. Courville reported a case involving the posterior fossa; the infection had apparently begun in the leptomeninges, fusing the dura, arachnoid and pia and adjacent portions of the cortex into a continuous mass of organized exudate. Microscopically this showed typical tuberculous granulation tissue.

There is little difficulty in differentiating the tuberculous forms for what they are.

Neoplastic Origin.—We shall mention the fourth large category—i. e., the neoplastic group—only to say that the microscopic study differentiates those cases of dural thickening grossly confused with the conditions heretofore discussed (Dumas and Nolan,[76] Henschen [46] and Russell and Cairns [77]). With this group we may mention the rare case of xanthomatosis affecting the dura reported by Pinkus and Pick.[78]

Spinal Pachymeningitis.—Spinal pachymeningitis requires mention in view of our discussion of cases of obscure origin, and the cases of syphilitic origin fuse imperceptibly with those for which no cause can be found. As in infections of the cranial dura, those cases of tuberculous

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73. Grosz, K.: Klinische und Liquordiagnostik der Rückenmarkstumoren, Wien, J. Springer, 1925, cited by Wiersma.[58]

74. Miller, E.: Case of Pachymeningitis Cervicalis of Syphilitic Origin, Proc. Roy. Soc. Med. **12**:55, 1918-1919.

75. Tooth, H. H.: A Case of Dorsal Pachymeningitis, Brain **7**:254-258, 1884-1885.

76. Dumas, A. G., and Nolan, L. E.: Carcinomatosis of Meninges Simulating Pachymeningitis Hemorrhagica Interna: Report of a Case, J. Nerv. & Ment. Dis. **83**:547-556 (May) 1936.

77. Russell, D., and Cairns, H.: Subdural False Membrane or Hæmatoma (Pachymeningitis Interna Hemorrhagica) in Carcinomatosis and Sarcomatosis of Dura Mater, Brain **57**:32-48 (March) 1934.

78. Pinkus, and Pick, F., cited by Henschen.[46]

origin are readily identified; but we consider them when advisable for comparison.

In 1873 Charcot [79] and Joffroy [80] described a condition of the spinal meninges known as hypertrophic cervical pachymeningitis. Hirtz [81] felt that the earlier cases of Gull in 1858 and Koehler in 1861 might fall into this group but that Charcot and Joffroy established the entity in 1869 and in the immediate years thereafter. Charcot discussed the condition as being one of several inflammatory "neoplasms" capable of giving rise to slow spinal compression. He felt that some of those cases which previously had been called hypertrophy of the cord probably were examples of this condition of pachymeningitis hypertrophica. The dura was seen to be composed of numerous concentric layers and was markedly thickened. At times the dura seemed separated into an internal and an external layer. The former (internal) appeared to be a new formation composed of a dense fibroid tissue. Charcot drew the distinction between this dural change and the neomembranes which in the spinal and cerebral dura are associated with hematomas. The chronic inflammation might give rise to a thickening of 6 to 7 mm.

Paviot and associates [82] broke down the cases of cervical hypertrophic pachymeningitis into etiologic groups: those due to tuberculosis, those due to syphilis and those associated with syringomyelia. There was a group left over of unknown origin, and the authors presented a case of this class in which operation was done. The dura was thickened and roughened on the exterior surface and was vascular. The inner surface of the dura was normal. The inflammatory reaction consisted of polymorphonuclear cells, lymphocytes, plasma cells, macrophages and blood pigment. It had formed a sclerotic epidural investment, fused with the otherwise normal dura (compare with sclerogummatous form of cerebral pachymeningitis previously mentioned). It will be seen that in this case the changes were primarily on the external surface of the dura, unlike the description by Charcot and Joffroy of alteration of the internal surface. Siebner [83] presented a case of long-standing

79. Charcot, J. M.: Lectures on the Diseases of the Nervous System (translated by George Sigerson), London, The New Sydenham Society, 1889, vol. 3, pp. 125-129; Pachyméningite cervicale hypertrophique, Gaz. d. hôp. **60**:890-892, 1887.

80. Joffroy, A.: De la pachyméningite cervicale hypertrophique, Thèse, Paris, no. 79, 1873.

81. Hirtz, E.: De la pachyméningite cervicale hypertrophique curable, Arch. gén. de méd., Paris **157**:641-658, 1886.

82. Paviot, J.; Wertheimer, P.; Dechaume, J.; Levrat, M., and Jarricot, H.: Pachyméningite cervicale hypertrophique d'origine indéterminé, Lyon méd. **149**: 613-620 (May 15) 1932.

83. Siebner, M.: Pachymeningitis cervicalis hypertrophica und akute Schädigung durch Myelographie, Chirurg. **7**:177-180 (March 15) 1935.

cervical hypertrophic pachymeningitis, the acute clinical phase of which had been precipitated by myelography. This was presented as an example of Charcot's form. The cervical dura was markedly thickened. The dense, poorly cellular connective tissue and collagen were infiltrated with nests of lymphocytes, and perivascular infiltrations were present. The thickening had included the pia. The subdural space was obliterated, but there was some fat deposition between the connective tissue septums. A fresh exudative process on the surface of the old dural thickening was also described. This writer felt that the disease could be more or less circumscribed or could be general, covering the whole spinal pachymeninx. He listed the etiologic factors as syphilis, tuberculosis, an acute infectious disease (unqualified), a metastatic infection and trauma.

That a similar process might occur elsewhere than in the cervical region is understood. The cervical and upper thoracic form was presented by Déjerine and Tinel.[84] Their case, unassociated with cerebral pachymeningitis, was of syphilitic origin. The appearance simulated that of a cerebral tumor. The dura was from 2 to 7 mm. in thickness in the cervical regions and 1 to 2 mm. in thickness about the brain stem. A lamellated fibrous tissue with small gummas was seen microscopically, and characteristic vascular changes were evident. The midthoracic form was described by Krause,[85] Tooth [75] and others. Runge,[86] for example, presented a case showing hardened and thickened dura from the third to the fifth thoracic segment, but the dura was involved on its external surface in a red-brown fibrinous exudate. Runge could not find evidence to blame syphilis or tuberculosis for the change, which he called a primary one. The lumbar form was reported by Foix, cited by Moniz,[87] and the generalized distribution was covered by the cases of Mills and William [88] and Mills and Spiller.[89] With regard to frequency in these locations, Ody [90] felt that the condition occurred

84. Déjerine, J., and Tinel, J.: Un cas de pachyméningite cervicale hypertrophique, Rev. neurol. **17**:240-244, 1909.

85. Krause, F.: Indurations of the Spinal Cord (Meningitis fibrosa Chronica) in The Surgery of the Brain and Spinal Cord, translated by Max Thorek, New York, Rebman Company, 1912, vol. 3, pp. 1103-1124.

86. Runge, W.: Beitrag zur Frage der Pachymeningitis dorsalis Zusammenhang mit Trauma, Aerztl. Sachverst.-Ztg. **26**:61-66, 1920.

87. Moniz, E.: La pachyméningite spinale hypertrophique, Rev. neurol. **32**:433-463, 1925.

88. Mills, C. K., and William, E. M.: Chronic Hypertrophic Spinal Pachymeningitis, J. Nerv. & Ment. Dis. **38**:705-719 (Dec.) 1911.

89. Mills, C. K., and Spiller, W. G.: Case of External Spinal Pachymeningitis Implicating the Entire Ventral Surface of the Spinal Dura, Brain (pt. 3) **3**:318, 1902.

90. Ody, F.: Notes sur un cas de pachyméningite (opéré avec succès), Rev. méd. de la Suisse Rom. **50**:221-230 (March 25) 1930.

most frequently in the cervical region and was much commoner in the thoracic region than in the lumbar area.

Tooth's description [75] of the thoracic dura was of interest. The tough mass he found was 5 mm. thick and included the fused pia-arachnoid. The component bundles of connective tissue were separated by large numbers of leukocytes. The vessels were numerous but without particularly thickened walls. Between the dura and pia was a mass of fibrous material making up about four fifths of the whole thickness. This consisted in its outer three fourths of bundles of large wavy structureless fibers, running in all directions but mostly parallel to the fibers of the dura. There were numerous lacunae containing nuclei but no vessels. As the inner boundary was reached, the fibers became smaller and the lacunae larger, containing numbers of leukocytes. Here there were numerous blood vessels with thickened walls. The author felt that the state probably originated as a gumma of the dura which subsequently took on a fibroid character. Some of the early reported cases, such as those of Remak,[91] Berger,[92] Gibney,[93] Suckling [94] and, later, Watkins [95] under the heading of cervical hypertrophic pachymeningitis, presented clinical aspects only and were unverified by either operative or autopsy examination. The case report by Glynn [96] was unaccompanied with careful microscopic study. The same statement is true of Gilpin's case,[97] although in it the patient had a thickened and leathery dura; the condition was considered to be due to trauma. Miller's [74] case cannot be included in our study, for it had neither surgical nor autopsy confirmation. Munson [98] classified his case with those of Charcot, but the cerivcal portion of the patient's dura was thickened and attached firmly to the neighboring vertebrae. It was not adherent to the arachnoid. Careful microscopic analysis was not reported, and the cause in this case remained obscure.

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91. Remak, E.: Ueber einen Fall von abortiver Pachymeningitis cervicalis hypertrophica, Deutsche med. Wchnschr. **13**:572, 1887.

92. Berger: Zur Kenntniss der Pachymeningitis spinalis hypertrophica, Deutsche med. Wchnschr. **4**:619; 630 and 643, 1878.

93. Gibney, V. P.: Cervical Pachymeningitis: The Detailed Histories of Three Cases Occurring in Children, M. Rec. **18**:341-346, 1880.

94. Suckling, C. W.: Case of Pachymeningitis Cervicalis Hypertrophica, Brain **8**:91-93, 1885.

95. Watkins, A. M.: Pachymeningitis cervicalis hypertrophica, M. J. Australia **2**:88-89 (July 26) 1924.

96. Glynn, T. R.: Internal Hypertrophic Pachymeningitis of the Cord, Brit. M. J. **2**:805 (Nov. 30) 1878.

97. Gilpin, S. F.: Case of Traumatic Pachymeningitis, J. Nerv. & Ment. Dis. **45**:444, 1917.

98. Munson, J. D.: Pachymeningitis Interna Hypertrophica, Detroit Lancet **7**:536-538, 1883-1884.

Bertha and Fossel [99] applied the term "gummatous" to their case of obviously syphilitic orgin, in which the dura was 2 to 3 mm. thick, gray-white, smooth and firm. Carlill and Carling's [100] similar case may also be cited.

The case of Malherbe [101] was of syphilitic origin; it was a syphilitic pachymeningitis with a condensing osteitis affecting both the cranial and the spinal dura and including the sheaths of the cranial and spinal nerves. The reaction was on the surface of the dura. The dura was sprinkled with small tumor masses of syphilitic characteristics, but a careful histologic study was not reported. The 3 cases of Ricard, Dechaume and Croizat [102] of suspected syphilitic origin showed the dura to be from 5 to 8 mm. in thickness. It was lamellated and hard to cut and showed perivascular inflammatory reactions of plasma cells, lymphocytes and a few polymorphonuclear cells. The pia and the arachnoid were unaltered. In 2 cases a sclerotic granulation tissue on the outer surface of the dura gave the appearance of a fungoid mass, and in the 1 case which was least likely to be due to syphilis there was a predominance of eosinophils infiltrated throughout the reacting dura.

Gowers [103] felt that the syphilitic form of pachymeningitis affected the pia-arachnoid more extensively than did the other idiopathic forms and that the latter forms with dural change alone were, as Charcot indicated, due to cold, fatigue and trauma. In the hypertrophic syphilitic form which Stephenson [104] described, the process attacked the inner surface of the dura. The fibrous exudations took place between the dura and the cord itself. These exudates might become the consistency of osseous tissue. The 2 cases of Parachu and Castane [105] were also considered syphilitic in origin, and the 2 cases of Fischer [106] showed

99. Bertha, H., and Fossel, M.: Ueber einen Fall von Pachymeningitis cervicalis hypertrophicans gummosa, Monatsschr. f. Psychiat. u. Neurol. **95**:102-112 (March) 1937.

100. Carlill, H., and Carling, E. R.: Disease of Cervical Spinal Cord, Lancet **1**:70-72 (Jan. 9) 1926.

101. Malherbe, J.: Observation de pachyméningite syphilitique, J. de méd. de l'ouest, Nantes **17**:251-257, 1883.

102. Ricard, A.; Dechaume, J., and Croizat, P.: Compression médullaire par pachyméningite hypertrophique post-traumatique, Lyon méd. **144**:93-162 (July 28) 1929.

103. Gowers, W. R.: Manual of Diseases of Nervous System, ed. 2, Philadelphia, P. Blakiston's Son, 1901-1902.

104. Stephenson, J. W.: Case of Pachymeningitis Spinalis with Thrombotic Softening, M. Clin. North America **8**:379-384 (July) 1924.

105. Parachu, L. M., and Castane, D.: Paquimeningitis cervical hipertrófica sifilítica con estudio histológica, Rev. argent. de neurol. y psiquiat. **1**:215-225 (June) 1935.

106. Fischer, O.: Zur Frage der Pachymeningitis interna chronica cervicalis hyperplastica, Ztschr. f. Heilk. **25**:339-351, 1904.

chronic hyperplastic changes of the dura and leptomeninges in the cervical region. In 1 of these cases, associated with secondary softening of the central nervous system, there were vascular changes in the pia suggestive of syphilis. The reaction of the arachnoid and inner surface of the dura was regarded as secondary. The second case showed changes limited to the meninges, and the author suggested that the term hyperplastic rather than hypertrophic be applied to this example of what he thought was Charcot's entity.

In Wiersma's case [58] there was marked compression of the cord by the hypertrophic dural formation in the thoracic region. There was a mass of detritus beneath the dura, and the meninges were fused and highly thickened. They were composed for the greater part of granulation tissue in which many exudation cells and marked hyperemia pointed to the inflammatory character of the process. This writer stated that, although syphilis was a common cause of such a change, it was by no means essential in the production of the changes. In his case he found no evidence of syphilis.

A dense cicatricial mass of fibrous tissue involving the dura surrounded the cord in the case of Ody [90] in which operation was done. He found some areas of degeneration and perivascular lymphocytic infiltration in the hyperplastic dura. He separated the type of Charcot and Joffroy from the types due to tuberculosis and syphilis, and he recognized secondary hypertrophic dural changes associated with Pott's spondylitis. Tinel and Papadato [107] recognized the etiologic factors in the production of cervical hypertrophic pachymeningitis to be primarily syphilis and tuberculosis. In the case of Rumke and Goudsmit,[108] in which operation was done also, the changes in the dura were reported to be on the basis of tuberculosis. Vulpian,[109] without a careful pathologic critique, felt that these cervical dural changes were secondary to a chronic meningitis in which all three meninges were bound together. As etiologic factors he indicated Pott's spondylitis and venereal disease, syphilis in particular. The case of Bernard, Hermange and Delcour [110] demonstrated the role of tuberculosis in the causation of hypertrophic changes of the spinal dura. In their case with operation all the meninges of the upper thoracic region were bound together in a thick, homogeneous scar. The microscopic picture showed marked

107. Tinel, J., and Papadato, L.: Étude anatomo-pathologique de la pachyméningite cervicale hypertrophique, Progr. méd., Paris **29**:377-381, 1913.

108. Rumke, H. C., and Goudsmit, J.: Treatment of Cervical Hypertrophic Pachymeningitis, Nederl. tijdschr. v. geneesk. **71**:2854-2860, 1927.

109. Vulpian, A.: Pachyméningite cervicale hypertrophique, Clin. méd. d. l'hôp. de la Charité **8**:791-807, 1879.

110. Bernard, A.; Hermange, M., and Delcour, J.: Tuberculous Cervical Pachymeningitis, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1277, 1927.

lymphocytic infiltration, areas of caseation with peripheral zones of fibrous tissue and giant cells. They found, in contrast to the relative frequency of syphilitic pachymeningitis, pachymeningitis secondary to syringomyelia (of which we will speak later) or pachymeningitis secondary to Pott's disease, that primary cervical tuberculous pachymeningitis was rare. Grosz [78] cited 1 case in which tuberculosis caused a pure pachymeningitis without vertebral or other recognized involvement. The diagnosis cannot be substantiated in the case in which Goldie and Primrose [111] asserted that operation was successful. A discussion of the differential points between syphilitic pachymeningitis and that secondary to Pott's disease was given by Sicard and Cestan.[112] The tuberculous process of the dura was felt by these authors to be a far more limited one than the generalized syphilitic reaction.

As examples of a form similar to that of Charcot, Hohlbaum [113] presented 4 cases. The first was an instance of thickened dura with spinal block following meningococcic meningitis six months earlier. The dura was adherent to the periosteum and had to be separated from the cord by sharp dissection. In the second case the process occurred three years after spinal anesthesia. The dura was ten times normal thickness, and the dural sac was completely obliterated. Fibrous changes and chronic inflammation only were shown on microscopic examination. In his fourth case the picture was similar and was considered to have originated on a chemical basis. The third case was also presented as resulting from supposed meningitis nine years previously. No microscopic examination was given in these postmeningitic cases. Weigeldt [114] described obliteration of the subdural sac following lumbar puncture. The meninges were thickened and necrotic on the internal surface, being barely distinguishable from the substance of the cord.

Kment and Salus [115] operated on 3 patients and reviewed 16 cases from the literature. They offered a postmeningococcic meningitic state as one cause for a fibrous dural thickening with chronic inflammation dominated by plasma cells. Syphilis was another cause and trauma a questionable one in the other cases. These authors listed the etiologic

111. Goldie, W., and Primrose, A.: Case of Cervical Hypertrophic Pachymeningitis with Exploratory Laminectomy, Canad. Pract. & Rev. **34**:135-141, 1909.

112. Sicard, J. A., and Cestan, R.: Pachyméningite tuberculeuse et syphilitique, Bull. Soc. méd. hôp. de Paris **21**:725-729 (s. 3) 1904.

113. Hohlbaum, J.: Ueber Pachymeningitis adhesiva spinalis, Zentralbl. f. Chir. **57**:979 (April 19) 1930.

114. Weigeldt, W.: Rückenmarksschädigungen nach Lumbaranästhesien und Vuzininjektion (Obliteration des Subarachnoidealraumes), Deutsche Ztschr. f. Nervenh. **84**:121-131, 1925.

115. Kment, H., and Salus, F.: Pachymeningitis hypertrophica, Beitr. z. klin. Chir. **154**:191-210, 1931.

factors in spinal pachymeningitis. Tuberculosis and syphilis led the list; then came metastatic or neighborhood infections, and trauma was last. Kramer [116] reported a case of pachymeningitis affecting the thoracic region of the spine in which an epidural granulation mass of 10 mm. thickness was removed at operation. The dura beneath was 4 mm. thick. The mass histologically was fibrous with many round cells and leukocytes, a nonspecific picture. An acute inflammatory process eight years previously was offered as a possible related factor. In Küttner's [117] somewhat similar case there was a discrete epidural mass considered to be syphilitic in origin.

The formation of perimeningeal granulations caused by trauma and followed by degeneration of congenital syphilitic origin was offered as the mode of pathogenesis by Joisten [118] in his case. Laminectomy in the midthoracic region demonstrated a laminated epidural granulation fused indistinguishably with the dura, which was itself thick and pulseless. In the midportion a soft caseating mass was found (gumma?). Confluent epithelioid knots which went on to extensive caseation infiltrated the epidural meshwork. Kunze [119] also entertained the thought that trauma might give rise in certain cases to pachymeningitis. In his case of an epidural inflammatory meshwork the condition probably was secondary, however, to a pyemic decubitus ulcer. External pachymeningitis was classified by Runge [86] as due to (1) syphilis, usually involving the pia, but also the dura; (2) tuberculosis; (3) purulent meningitis; (4) metastatic foci, as from a pulmonary abscess; (5) unknown factors, in which trauma might play an etiologic role.

Ricard and associates [102] and Pomme and associates [120] cited cases of suspected traumatic origin. The case reported by the latter authors was one in which operation was performed ten years after trauma to the thoracic portion of the spine. The dura was markedly thickened with the primary reaction in the outer dural layer. Plasmacytes predominated. These authors agreed with Veraguth and Schnyder that all cases were secondary to more fundamental disease entities. The 2

116. Kramer: Ueber einen Fall von Pachymeningitis externa, Berlin. klin. Wchnschr. **48**:735, 1911.

117. Küttner, H.: Pachymeningitis Externa, Deutsche med. Wchnschr. **37**: 1500, 1911.

118. Joisten, C.: Ueber Pachymeningitis dorsalis hypertrophica, München med. Wchnschr. **74**:273 (Feb. 18) 1927.

119. Kunze, W.: Beitrag zur Frage der Pachymeningitis, Zentralorgan. f. Chir. **7**:319, 1920.

120. Pomme, B.; Ricard A., and Dechaume, J.: Compression médullaire par pachyméningite hypertrophique probablement post-traumatique, Lyon méd. **150**: 69-73 (July 17) 1932.

cases of traumatic pachymeningiosis reported by Jentzer [121] should be noted among the cases of spinal pachymeningitis.

The cases of purely epidural infection due to causes such as purulent collections are not considered here. We have seen that in the spinal dura, as in the cranial dura, there may be a neighborhood reaction on the part of the dura secondary to other infection, including tuberculosis of the spine. The epidural granulomas also are a distinct group (Baumert and Zech,[122] Dandy,[123] Dunn,[49] Elsberg,[124] Morawitz,[125] Schmalz,[126] Spencer,[127] Veraguth [128] and Watts and Mixter [129]).

The association between pachymeningitis of certain forms and medullary cavitation (syringomyelia) has been recognized (Micheev and Pavljutschenko,[130] Moniz,[87] Phillipe and Oberthur [131] and Tooth [75]). Micheev and Pavljutschenko [130] felt that the entity of pachymeningitis with associated medullary cavitation always occurred secondary to a specific disease, the most frequent and important being syphilis. Marinesco [132] in 1895 separated the idiopathic syringomyelia from the form secondary to cervical hypertrophic pachymeningitis. Moniz [87] presented a case of this cervical dural disease in which the dura was very thick and was stuck to the pia and there was some thickening of the latter. The reason for the association of syringomyelic cavities with pachymeningitis was not clear in this author's mind, but compression

121. Jentzer, A.: Duraverdickungen, traumatischer und nicht traumatischer, Arch. f. klin. Chir. **180**:432-442, 1934.

122. Baumert, W., and Zech, K.: Pachymeningitis externa spinalis, München med. Wchnschr. **87**:824 (Aug. 2) 1940.

123. Dandy, W. E.: Abscesses and Inflammatory Tumors in Spinal Epidural Space (So-Called Pachymeningitis Externa), Arch. Surg. **13**:477-494 (Oct.) 1926.

124. Elsberg, C. A.: Dorsal Pachymeningitis Cured by Laminectomy, Ann. Surg. **62**:101, 1915.

125. Morawitz, P.: Ueber akute eitrige Perimeningitis, Deutsche Arch. klin. Med. **128**:294-316, 1919.

126. Schmalz, A.: Ueber akute Pachymeningitis spinalis externa, Virchows Arch. f. path. Anat. **257**:521-560, 1925.

127. Spencer, W. H.: Case of Idiopathic Inflammation of the Spinal Dura Mater (Pachymeningitis Spinalis Externa), Lancet **1**:836 (June 14) 1879.

128. Veraguth, O.: Peripachymeningitis spinalis chronica nonspecifica: Operation—weitgehende Besserung, Schweiz. med. Wchnschr. **10**:154-158 (Feb. 16) 1929.

129. Watts, J. W., and Mixter, W. J.: Spinal Epidural Granuloma, New England J. Med. **204**:1335-1344 (June 25) 1931.

130. Micheev, W. W., and Pavljutschenko, E. M.: Zur Frage der Pachymeningitis cervicalis hypertrophica, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**: 797-803, 1928.

131. Phillipe, C. P., and Oberthur: Classification des cavités pathologiques intramédullaires, Rev. neurol. **8**:171-175, 1900.

132. Marinesco, G.: Contribution à l'étude de la pachyméningite hypertrophique, Rev. neurol. **23**:233-253 (Oct.) 1916.

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was considered the probable cause. Moniz felt, as did Papadato,[133] that the cause in these cases involving the spine was tuberculosis or syphilis. He entertained the possibility that a neoplastic process might explain some cases, and there remained a questionable idiopathic form. Bernard and colleagues[110] reported cavitation similar to syringomyelia in their case of tuberculous pachymeningitis. The cavities existed below the level of compression of the cord, however, and they emphasized the importance of the concommitant occurrence of cervical pachymeningitis of hypertrophic form. They did not feel that there was necessarily any etiologic relationship. In the cases of Thomas and Hauser[134] the condition was secondary to Pott's disease. Uprus and Ley[135] considered the cavities secondary to compression, and they cited Aschoff as being of the opinion that the cavities were due to a true meningomyelitis, the pachymeningitis and the syringomyelia following as the pathologic state developed.

Uprus and Ley,[135] as well as Wilson, Bartle and Dean,[136] accepted an idiopathic form of spinal hypertrophic pachymeningitis, although the condition in the vast majority of cases they explained as due either to tuberculosis or to syphilis. Courville[28] classified hypertrophic cervical pachymeningitis as a syphilitic process consisting in a proliferation of granulation tissue arising from the inner dural surface or resulting from a syphilitic reaction of the dura itself causing a tremendous thickening. Other remote and highly questionable causes for the process were listed by Cassirer,[137] Babonneix and Voisin[138] and others previously noted.

SUMMARY

An unusual case of hypertrophic pachymeningitis simulating a cerebellar tumor is presented, with a review of the literature. The various causes of the dural inflammatory reactions are discussed.

The definitely infectious groups of pachymeningitis have been reviewed, including the cases due to specific infections, viz. syphilis and

133. Papadato, L.: Contribution to the Study of Pachymeningitis Cervicalis Hypertrophica, Thèse, Paris, no. 433, 1912.

134. Thomas, A., and Hauser, G.: Cavités médullaires et mal de Pott, Rev. neurol. **9**:117-127, 1901.

135. Uprus, V., and Ley, A.: Estudio anatomoclinico de un caso de paquimeningitis espinal hipertrofica, Rev. d. cir. de Barcelona **4**:489, 1932.

136. Wilson, G.; Bartle, H. D., Jr., and Dean, J. S.: Chronic Hypertrophic Spinal Pachymeningitis, Am. J. M. Sc. **198**:616-622 (Nov.) 1939.

137. Cassirer, R.: Pachymeningitis cervicalis hypertrophica, in Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1923, vol. 1, p. 420.

138. Babonneix, L., and Voisin, R., cited by Wiersma[58]: Méningites chroniques, in Sergent, E.; Ribadeau-Dumas, L., and Babonneix L.: Traité de pathologie médicale et de thérapeutique appliquée, Paris, A. Maloine et fils, 1925, vol. 5, p. 606.

tuberculosis. A distinction has to be made bacteriologically between true infections of the dura by pathogenic organisms and sterile reactions to outside infections. We have divided the cases of cerebral dural involvement from the cases of spinal involvement merely as a matter of convenience; an artificial distinction should not be made. From the case presented in this paper it is evident that both spinal and cranial dura may be heir to the same disease process, although in the literature few descriptions of combined involvement are found; Malherbe's case [101] is an example.

Hemorrhagic manifestations are rarely reported as implicating the spinal pachymeninx. The differences in anatomy, particularly in vascular distribution, may explain this fact.

The problem of pachymeningitis of obscure and unknown origin both in the cranium and in the spinal canal has fused with the consideration of the other groups of better defined conditions. There have been reviewed states and cases in which the cause was not uncovered to our satisfaction. We feel that the case presented in this paper was one in which the pachymeningitis was due to a sterile inflammatory neighborhood reaction on the part of the dura to recurrent external infections. These infections may have given rise to osteitis or indeed osteomyelitis, but this process was not demonstrated pathologically.

Dr. Henry Kempe assisted with part of the German translations.

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BRAIN WAVE PATTERNS DURING HYPNOSIS, HYPNOTIC SLEEP AND NORMAL SLEEP

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CHARACTERISTIC patterns of brain waves can be recorded during various levels of sleep, normal or narcoleptic, and in coma or coma-like states. In short, any reduction of consciousness below the waking level is reflected in the brain wave pattern. The electroencephalogram is thus an indicator of the sleep–wakefulness level prevailing during any particular organism-environment relationship.

Hypnosis is a particular form of organism-environment integration about which interest has recently been reawakened. Relatively rapid changes between wakefulness and sleep may be effected by hypnosis. Characteristic changes in the brain wave pattern should accompany these behavioral changes during hypnosis. Investigators who have recorded the encephalogram during hypnosis have, however, reported only slight differences between waking and hypnotic patterns [1] or none at all.[2] Dynes published records which show no discernible change in the encephalographic pattern as the subject passed into a hypnotic trance.[2] He stated, "The objective evidence presented here confirms the opinions of investigators who have claimed that hypnosis is not a sleep variant."

Various changes in somatic function produced by hypnotic suggestion have been reviewed by Kleitman.[3] Similar changes have, however, been produced during so-called waking hypnosis.[3] And, finally, many hysterical and schizophrenic patients exhibit somatic reactions

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1. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Electrical Potentials of the Human Brain, J. Exper. Psychol. **19**:249, 1936.

2. Dynes, J. B.: An Objective Method for Distinguishing Sleep from the Hypnotic Trance, Arch. Neurol. & Psychiat. **57**:84 (Jan.) 1947.

3. Kleitman, N.: Sleep and Wakefulness, Chicago, The University of Chicago Press, 1939.

quite like those produced by hypnotic suggestion. Thus, reduction of wakefulness to sleep levels seems not at all essential for the occurrence of these somatic reactions.

Considerable confusion has arisen from the failure to differentiate between hypnotic sleep and hypnotic suggestibility. Thus, Dynes [2] has defined "trance" as a hypnotic state in which there are amnesia for its events and anesthesia for painful stimuli and in which effective post-hypnotic suggestion may be given. These are criteria for suggestibility, not necessarily for a stage of sleep. However, it is on the failure to observe electroencephalographic changes between waking and the "trance" state, into which the subject passed at the signal of a finger snap, that Dynes based his conclusion, previously quoted, that "hypnosis is not a sleep variant."

The question arises, how does one ascertain whether a subject is asleep or awake? In all other forms of behavior, the electroencephalogram provides adequate criteria for differentiating sleep from wakefulness. Hence, if the hypnotic subject has closed his eyes and appears to be asleep but no changes from the waking alpha pattern are observed the subject is not asleep—or else the hypnotic variety of sleep involves neurophysiologic processes entirely different from those of other forms of sleep.

Previous investigations have largely been concerned with electroencephalographic changes associated with suggested alterations in particular somatic functions. It seemed desirable to ascertain whether sleep accompanied with typical brain wave patterns might not be directly produced by hypnotic suggestion. This communication reports the production during hypnosis of various stages of sleep accompanied with electroencephalographic sleep patterns.

METHOD

This study is based on results of several experiments, each of which was successful. The electroencephalographic patterns of the first 4 subjects studied will be illustrated. Similar patterns were obtained in other experiments.

Each patient was seated in a semireclining chair, a not particularly comfortable one, and needle electrodes were placed for double scalp recording. A vertex electrode was used as a common lead. A control record was obtained, without hyperventilation at this time, and induction of hypnosis was begun.

Our method of hypnosis can be characterized by stating the assumptions on which it is based. The integration of an organism with its environment is carried out by the central nervous system with the cerebral cortex as the primary organizer of perception-response patterns. Contemporary reality is interpreted in the light of past experience, and sensory exploration is directed in the service of the subject's immediate goals.

Perception of distant reality involves primarily the use of the ears and eyes. Somatic reality is perceived, in the main, by means of sensory inflow from the skin, muscles and joints. In ordinary wakefulness or sleep, the central nervous

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system may shift its focus of activity through all the aspects of reality existing in memory, in the present, or, by projection, in the future.

The process of hypnosis, first of all, places great restrictions on the extent of reality. If the subject's active attention to the hypnotist's first remarks has been gained, conscious time is limited to the immediate present. When the subject's gaze is directed upward at a small bright object, distant reality is limited to the hypnotist's statements and the visual image of the object. If the subject sits without moving and is even only minimally relaxed, the bulk of general somatic stimuli is reduced or monotonized. Awareness is then dominated by the active, upward gaze, which involves tension of all the ocular muscles and hence masses of sensory inflow.

Thus, as the hypnotist urges the subject to become absorbed in looking at the small bright object, visual, auditory and somatic inflow become merged into one total "reality." And, as fatigue inevitably develops with this unusual oculovisual activity, it is from the totality of the existing reality that the subject requires relief. Hence, when the hypnotist says, "As you continue to look upward at the object, you will become increasingly tired and will want to close your eyes," he is at the same time accurately describing momentary reality in its entirety, predicting unerringly the immediate future, and "motivating" the subject to obey the prediction. Thus, the hypnotist's statements have become identical with reality!

If the subject remains passive and refrains from "reality-testing" through active "consensual-validation," he will have no choice but to accept succeeding statements as equally valid if they pass from "truth" to "falsity" in a smooth sequence.

It is essential that the "truth" of the first statements depend not so much on the authoritative manner of the hypnotist or the willingness of the subject to accept authority as on their own correspondence to the restricted, but objective, reality remaining for the subject. Difficulties arise at those critical points when statements and predictions contain a large element of objective "falsity." The subject is told, "You are going to close your eyes," the first time he starts to do so spontaneously. In the course of other, and well known, maneuvers, such as collapse of the upright forearm and extended hand, inability to open the tightly interlaced fingers and so on, any "testing" reactions or other movements are utilized in the "predictions." Consequently it is not too important whether the patient is otherwise "resistant" as long as he cooperates to the extent of the fixation of gaze.

When hypnotic suggestibility sufficient to produce paralysis, anesthesia and other reactions not involving sleep as such has been established, the induction of sleep is begun.

Recording of the electroencephalogram was begun at the very start of hypnosis in order that the subject would become accustomed to the noise of the oscillographs and writing pens. The records to be illustrated are all from the right occipital-vertex lead. Filtration was the same for each record. Differences in amplification are given in each figure. All the subjects were right handed; consequently the alpha patterns shown are from the nondominant hemispheres.

OBSERVATIONS

During induction of heaviness of the eyelids, the electroencephalographic pattern was that of low voltage, fast frequency waves observed ordinarily with the eyes open. Immediately the subject's eyes closed,

alpha waves appeared in the electroencephalogram and remained almost constantly present during the production of hypnotic suggestibility. Our subjects all had "alpha dominant" patterns—that is, alpha waves were present in control records almost 100 per cent of the time. In no case were waking control records characterized by "null" or other waves like those to be described as occurring during hypnotic sleep.

During hypnotic suggestibility—in which paralysis, anesthesia and such phenomena could be observed—alpha waves frequently diminished or disappeared for a few seconds in the brief interval between a given suggestion and its execution by the subject. This anticipatory "nulling" of the alpha waves was not an invariable reaction. It and other changes in brain wave patterns associated with specific suggestions or reactions involving somatic states will be illustrated and discussed in a subsequent paper.[4]

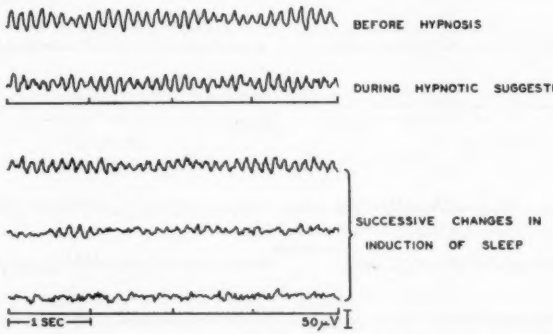

Fig. 1.—Brain waves of an epileptic subject before and after the induction of hypnosis are shown in the upper two lines. The decrease in alpha and appearance of the low voltage, fast frequency "null" pattern are shown in the lower three lines. Note that reduction of amplitude precedes the diminution in per cent of time that alpha waves are present. Filtration and amplification were constant throughout. The patterns, taken as samples from a continuously changing record, do not, of course, show the many minor gradations which actually are observed. All strips were taken from the right occipital-vertex channel.

In the upper two lines of figure 1, it can be seen that there is little if any difference between alpha patterns before hypnosis and those during hypnosis defined in terms of hypnotic suggestibility for somatic reactions not directly involving reduction of wakefulness as such. When specific suggestions designed to reduce wakefulness by minimizing the effect of sensory inflow were given, their effectiveness was reflected in the electroencephalogram by diminution of amplitude and percentage of alpha activity or by its disappearance. The relation between specific

4. Barker, W., and Burgwin, S.: Brain Wave Patterns Accompanying Changes in Sleep and Wakefulness During Hypnosis, Psychosom. Med. **10**:317 (Nov.-Dec.) 1948.

suggestions and associated electroencephalographic patterns will be described in detail elsewhere.[4]

Complete muscular relaxation and maximum "hypesthesia" to sensory inflow were sought by suggestions specifying particular body structures or functions. The subject was then told that he would hear only the hypnotist's voice, that it would become more and more indistinct and that he would accordingly pass deeper and deeper into sleep. Successive changes in the alpha pattern accompanying the induction of sleep are shown in the last three lines of figure 1. Similar brain wave changes have been observed in this subject, an epileptic patient, during normal sleep and during that occurring as a response

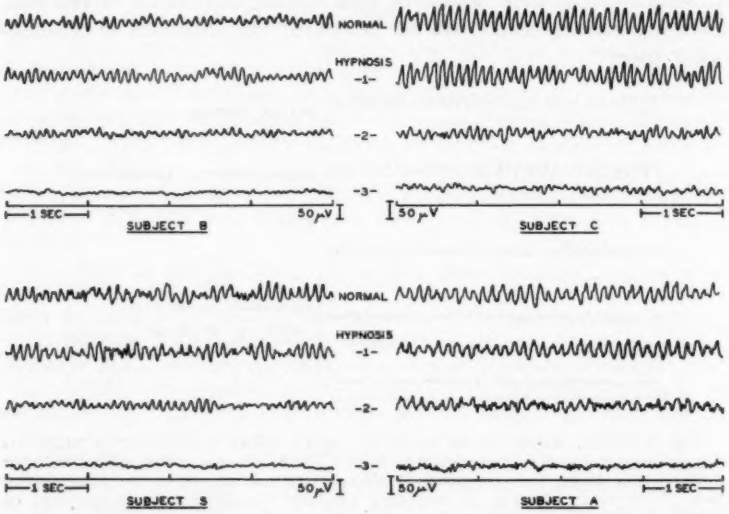

Fig. 2.—Samples taken from the continuous records of 4 normal subjects during the induction of hynotic sleep. The first two lines of each record show the similarity of the alpha patterns before and after the induction of hypnosis. The lower two lines of each record show the changes in pattern accompanying the induction of hypnotic sleep. The changes observed were, of course, not as abrupt as the isolated strips would indicate. The changes observed were relatively gradual. Spindling of the alpha waves, described by Davis [10a] in the onset of normal sleep was observed in several experiments as the first notable change in the alpha patterns. The low voltage, fast frequency waves seen in the last line of the record of subject A was seen at some time or other in the records of all subjects during the null phase.

to stress in amytal interviews.[5] The same patterns have been observed in normal and in narcoleptic sleep of narcoleptic patients.[6]

5. Barker, W.; Burgwin, S., and Simons, D. J.: The Significance of "Spontaneous" Abnormalities in Brain Wave Patterns as Observed During Interviews with Epileptic Patients, J. Nerv. & Ment. Dis., to be published.

6. Barker, W.: Personality Pattern, Situational Stress, and the Symptoms of Narcolepsy, Psychosom. Med. **10**:193 (July-Aug.) 1948.

The success of these efforts made it desirable to ascertain whether sleep and associated brain wave changes might not be induced in normal subjects. The results illustrated in figure 2 were obtained during hypnosis of students and physicians. In each case, the induction of hypnotic suggestibility, as such, was accompanied with no significant changes from the prehypnotic alpha patterns except for the brief "anticipatory" nulling previously noted. The first two lines of each subject's record show the alpha patterns before and after the induction of hypnosis.

However, when reduction of the sensory relationship with the environment and extensive muscular relaxation were suggested and effort directed to the induction of sleep, alpha patterns diminished and disappeared. The last two lines of each record in figure 2 illustrate this electroencephalographic reaction accompanying the induction of sleep.

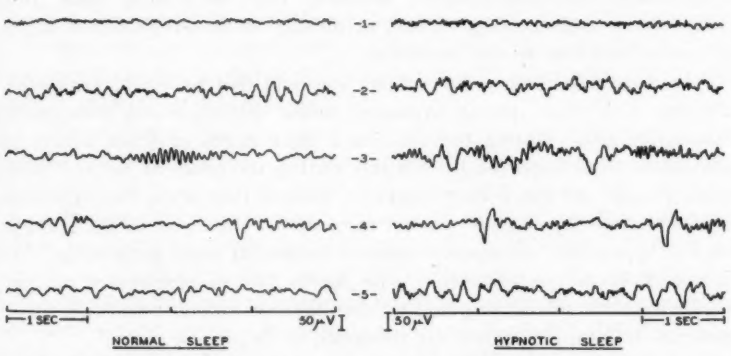

Fig. 3.—Comparison of the deeper sleep brain wave patterns observed during hypnotic sleep with similar patterns observed in normal sleep of the same subject. Note that amplification during hypnotic sleep was greater than that used during the normal sleep record. The C waves of lines 3 and the large slow waves of lines 5 are typical of deep sleep. The significance of the K waves seen in line 4 is not entirely clear. It is not the purpose of this illustration to describe "stages" of sleep during hypnosis but simply to indicate that waves typical of the deep stages of normal sleep may be observed in sleep produced hypnotically.

These observations demonstrate beyond doubt that alpha waves can be readily altered when hypnotic suggestions are concerned with functional states of the central nervous system in which electroencephalographic changes might be expected.

Patterns typical of deeper stages of normal sleep were also observed as a result of hypnotic suggestion. Figure 3 illustrates patterns of brain waves obtained from a subject during normal and hypnotically induced deeper stages of sleep. These patterns were observed subsequent to the "null" stage illustrated in line 1 of figure 3 as well as in the lower lines of preceding figures.

COMMENT

Definite stages are more readily observed during normal sleep than during that induced hypnotically because of the nature of the hypnotic situation. The hypnotic situation is esentially a special form of interpersonal relationship, and the phenomena which occur within it are thus a result of the interaction of the hypnotist and the subject, as Kubie and Margolin have emphasized.[7] Normal sleep is a state of reduced interaction with the environment characterized by the absence of contemporary interpersonal relationships. Hypnosis involves the reduction of organism-environment integration to a thin line of interpersonal communication. Since it is through this contact that the subject's reactions are "controlled," relatively continuous communication is necessary to maintain the hypnotic state at the sleep level; otherwise the subject tends to awaken. The time elements are therefore compressed. Persons sleeping normally may, of course, pass from wakefulness to deep sleep without exhibiting all the intermediate stages of sleep described in the literature.

In these experiments the subject was told that he would remember all that took place during hypnosis; hence subjective reactions could be ascertained. During the onset and light stages of sleep, reactions similar to those reported by subjects during the onset of normal sleep were noted. In the deeper stages, it seemed that when the hypnotist spoke to the subject there was no memory for the event or the content of the hypnotist's statements, unless changes in state were called for intentionally or inadvertently. The significance of changes in content of the hypnotic relationship and its simultaneous influence on brain wave patterns will be illustrated and discussed in detail elsewhere.[4]

The relation between hypnosis and certain psychopathologic states, on the one hand, and between hypnosis and sleep, on the other, has long been a controversial topic. The similarity of paralyses, anesthesias and other reactions produced by hypnotic suggestibility to those occurring at other times has been noted earlier. Since these reactions in other circumstances are not associated with any particular brain wave patterns, there is no reason to expect that their hypnotic production should be accompanied with sleeplike patterns in the electroencephalogram. The dynamics of these phenomena do not involve central nervous system operations reflected by specific brain wave changes.

But sleep, however produced, is a state of organism-environment integration involving major changes in central nervous system status in which characteristic brain wave patterns are observed. If it occurs during hypnosis, typical electroencephalographic changes should appear.

7. Kubie, L. S., and Margolin, S.: The Process of Hypnotism and the Nature of the Hypnotic State, Am. J. Psychiat. **100**:611, 1944.

Since the first hypnotic suggestions usually are designed to "put the subject to sleep" before other suggestions are given, it has perhaps been assumed that sleep is the first stage of hypnosis. Consequently, when electroencephalographic patterns in these circumstances are reported to be unchanged from those prevailing prehypnotically, confusion arises.

When it is stated [8] that "it is difficult to come to any other conclusion than that sleep is not hypnosis and that hypnosis is neither a suggested sleep nor a modified sleep nor anything between sleep and the normal waking state," it is essential to know exactly what is meant by "hypnosis." Similarly with Dynes's statement that "hypnosis is not a sleep variant."

Kleitman [3] attempted to resolve the confusion by stating that "it [hypnosis] is a state of hyperexcitability which by appropriate means can be lowered so much as to change it into a depression resembling sleep or narcosis. It sometimes passes into real sleep, thus creating confusion concerning the relation of these states to each other." This statement implies a distinction between "real" sleep and that which might appear during hypnosis.

The evidence which we have presented seems to clarify the nature of the relation between sleep and hypnosis. A comparison of alpha patterns prior to and after the induction of hypnotic suggestibility reveals, as previously reported by others,[9] no marked dissimilarities. This suggestibility, quite like that of the "trance" defined by Dynes,[2] could be produced without once mentioning sleep. Occasional brief disappearance of alpha activity was noted in connection with some suggestions. Our findings in this regard were somewhat different from those reported by Lundholm and Löwenbach,[9a] who described similar changes. The reasons for the differences are discussed elsewhere.[4] These brief "null" reactions are noted here simply to indicate that they played no part in the "null" sleep stages described in this paper.

It is perfectly clear, however, that when the hypnotic effort was turned from production of specific somatic reactions to the induction of sleep, typical electroencephalographic changes occurred. Alpha waves disappeared and were succeeded by characteristic sleep patterns; hence, characteristic changes were taking place in the central nervous system. Communication necessary to establish effective suggestions could be carried on during the presence of "null" activity, of low voltage, fast waves or of slow waves of about 5 per second frequency. However, it

8. Bass, M. G.: Differentiation of the Hypnotic Trance from Normal Sleep, J. Exper. Psychol. **14**:382, 1931.

9. (*a*) Lundholm, H., and Löwenbach, H.: Hypnosis and the Alpha Activity of the Electro-Encephalogram, Character & Personality **11**:145, 1942. (*b*) Loomis, Harvey and Hobart.[1] (*c*) Dynes.[2]

did not seem possible to maintain active communication with the subject and maintain deep sleep as indicated by the presence of C waves and larger random slower waves. These deeper stages could, nevertheless, be induced or terminated by appropriate suggestion. It thus seems clear that, while deep sleep is inconsistent with active organism-environment or interpersonal relations, whether during hypnosis or otherwise, deep sleep accompanied with characteristic brain wave patterns can be produced by hypnotic suggestion. In this sense, Kleitman's statement that hypnosis may pass into real sleep seems an adequate description of the dynamic relation between the two states.

Thus, however profound the changes in bodily state during hypnosis, if similar changes in other circumstances are not accompanied by typical brain wave patterns, there will be no particular changes in the electroencephalogram accompanying the hypnotic bodily reactions. Since the electroencephalogram in our experiments revealed brain wave patterns characteristic of all other forms of sleep,[10] it would seem logical to conclude that if the electroencephalogram during hypnosis does not record similar patterns the subject is not asleep.

Our results indicate that sleep is a state of reduced integrative interaction of the organism with its environment and that sleep may be produced by reducing, hypnotically or otherwise, the integrative activity of the central nervous system.

SUMMARY AND CONCLUSIONS

Brain wave patterns have been studied during hypnosis.

The "trance" state and suggestibility for reactions other than sleep can be established without significant alteration in the brain wave pattern. This suggestibility is associated with sleep and typical brain wave sleep patterns only if it is directed toward reduction of organism-environment integration.

Sleep, indistinguishable electroencephalographically from normal sleep in various stages, may be produced by hypnosis.

Hypnosis and sleep are special forms of organism-environment integration characterized by reduction of the integrative activity of the central nervous system.

10. (*a*) Davis, H.; Davis, P. A.; Loomis, A. L.; Harvey, E. N., and Hobart, G.: Brain Potentials During the Onset of Sleep, J. Neurophysiol. **1**:24, 1938. (*b*) Barker.[6]

PERIPHERAL NERVE AND ROOT DISTURBANCES FOLLOWING VACCINATION AGAINST SMALLPOX

Study of Five Cases, Review of the Literature and Discussion of Related Entities

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REPORTS on complications of smallpox vaccination have been appearing in both the lay and the medical literature for generations and the conditions have included urticarial [1] and erythematous rashes, generalized vaccinia,[2] local ulceration, lymph node abscesses, gangrene, tetanus, nephritis,[3] purpura,[4] encephalitis,[5] myelitis [6] and peripheral

From the Neurological Institute of New York.

Read before the Philadelphia Neurological Society, Feb. 28, 1948.

1. Templeton, H. J.: Postvaccinal Cutaneous Reactions, J. A. M. A. **81**:2115 (Dec. 22) 1923. McClure, W. B.: Urticaria and Nervous Manifestations Following Revaccination, Chinese M. J. **44**:526-531, 1930.

2. Ross, R. A.: Generalized Vaccinia, in Virus and Rickettsial Diseases, Cambridge, Mass., Harvard University Press, 1940. Tedder, J. W.: Eczema Vaccinatum, Arch. Dermat. & Syph. **34**:1108 (Dec.) 1936. McKhann, C. F., and Ross, R. A.: Generalized Vaccinia and Eczema Vaccinatum, M. Clin. North America **22**:785, 1939. Brown, E. L.: Eczema Vaccinatum, Arch. Pediat. **61**:233-239, 1944. Rubenstein, A. D.: Eczema Vaccinatum, New England J. Med. **237**: 395-397, 1947. Jubb, A. A.: Generalized Vaccinia, Brit. M. J. **1**:91-94, 1943. Najumdar, N. J.: Generalized Vaccinia, Calcutta M. J. **41**:290, 1944.

3. Herbut, P. A.: Diffuse Glomerulonephritis Following Revaccination for Smallpox, Am. J. Path. **20**:1011-1019, 1944. Saldun, M. L.: Glomerulo nefritis difusa en primera fase, postvacunacion antivariolica, Arch. de pediat. d. Uruguay **3**:442-447, 1932.

4. Heaton, T. G.: Purpura Associated with Vaccination Against Smallpox, Canada M. J. **43**:593-594, 1940. Schwartz, A. B.: Postvaccinal Purpura, Am. J. Dis. Child. **30**:856-858 (Dec.) 1925. Traut, E. F.: Purpura Following Vaccination, Illinois M. J. **44**:35-36, 1923.

5. Armstrong, C.: Postvaccination Encephalitis, with Special Reference to Prevention, Pub. Health Rep. **47**:1553-1568, 1932. Newman, S.: Postvaccinal Encephalitis, J. Pediat. **3**:461-470, 1933. Flexner, S.: Postvaccinal Encephalitis and Allied Conditions, J. A. M. A. **94**:305-311 (Feb. 1) 1930. The Nature of Postvaccinal Encephalitis, editorial, ibid. **101**:1485-1486 (Nov. 4) 1933. Bastiaanse, F. S. van B.: Die in Holland beobachteten Fälle von Encephalomyelitis postvaccinalis bis zum 1. Januar 1929, Ztschr. f. d. ges. Neurol. u. psychiat. **134**:657, 1931.

6. Broadbank, T. W.: Postvaccinal Myelitis, J. A. M. A. **97**:227-228 (July 25) 1931. Peake, H. G.: A Case of Postvaccinal Transverse Myelitis, Roy. Army M. J. **53**:443-445, 1929. Territt, R. A., and Carrell, R. C.: Post Vaccinal Myelitis, J. A. M. A. **94**:793 (March 15) 1930. Mage, J.: Un cas de myélite

(Footnote continued on next page)

neuritis. It is with the last-mentioned entity that this paper is concerned. Whereas there have probably been over 700 reported cases of postvaccinal encephalitis, there are but 7 reported cases of postvaccinal "neuritis" found in the literature, nearly all of which are questionable. In the League of Nations report [7] and in that of a British committee reviewing the subject of the postvaccinal nervous system complications,[8] there is no reference to single or to multiple neuritides.

Because of the rarity of the condition, because of its striking clinical picture and its good prognosis and because the reported cases were not recognized by the referring physicians, it is thought that a presentation of 5 cases of disturbances of peripheral nerves and roots following smallpox vaccination is important. These cases occurred as a result of the mass smallpox vaccination program in New York city during the last week of March and the first two weeks of April 1947, during which period approximately 6,350,000 persons were immunized.[9] As no detailed description of involvement of peripheral nerves and roots secondary to smallpox vaccination can be found, the cases will be described in detail.

REPORT OF CASES

CASE 1.—*History.*—A 45 year old American-born white mail carrier was revaccinated on April 26, 1947, in the region of the left deltoid insertion, the first vaccination having been done successfully at the age of 7. A papule formed after several days, followed rapidly by formation of pustules and scabs. Twelve days following vaccination the patient was awakened by severe sharp localized pain in the left shoulder. At noon sharp localized pain developed in both buttocks. That afternoon he began to have severe sharp pain in the right shoulder; it was unrelieved by morphine. That evening the pain in the buttocks disappeared. The next day the patient first noticed that both of his arms were weaker than normal. From that time until the date of admission—a period of twelve days—the weakness progressed until his upper extremities were practically useless, there being complete paralysis of all muscles at the shoulder, nearly complete paralysis at the elbow and partial function of the hands. The family history revealed twin siblings; one brother had died in convulsions at the age of 7. There was no family history of allergic phenomena. The past medical history showed an allergic sensitivity to oats, a "nervous breakdown" in 1925 and a duodenal ulcer many years ago. The patient's diet was well balanced, and there was no history of alcoholism or exposure to toxic agents.

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7. Report of League of Nations Commission on Smallpox and Vaccination, League Publications, no. 739, Geneva, August 27, 1928.

8. Report of Ministry of Health Committee on Vaccination, London, His Majesty's Stationary Office, July, 1928.

9. Personal communication to the author from Samuel Frant, M.D., Deputy Commissioner of Health, City of New York.

Physical Examination.—The patient was admitted to the service of Dr. Henry Alsop Riley at the Neurological Institute of New York on May 20. At that time he was seen to be in severe distress because of pain. He had a crusted lesion 1 cm. in diameter in the region of the left deltoid. The temperature was 99 F. rectally, the pulse rate 100 and the respiration rate 22; the blood pressure was 160 systolic and 90 diastolic. There was a soft apical systolic murmur. Moderate tenderness in the upper portions of both trapezius muscles and a slight decrease in tone in both upper extremities were found. There was slight bilateral atrophy of the shoulder girdle muscles, most easily seen in the deltoids. There was marked weakness of both upper extremities, far more marked proximally, severer on the left and more marked in the extensors. Strength varied from 0 to 20 per cent of normal in the shoulder musculature, 10 to 30 per cent at the elbow and 20 to 50 per cent at the wrist and hand. There was minimal weakness at the left hip. The deep reflexes in the upper extremities were greatly decreased, while those in the lower extremities were present but less active on the left. The superficial reflexes were present and equal, and no abnormal reflexes were elicited. There were no signs of meningeal involvement. The cranial nerves were entirely normal. There was diminution of all modalities of sensation over the distribution of the fourth, fifth and sixth cervical nerves bilaterally, the left side showing greater involvement than the right.

Laboratory Studies.—Studies included a complete blood count, urinalysis, Kline test and determinations of nonprotein nitrogen, blood surgar, serum cholesterol and sedimentation rate, all of which gave normal values. Spinal fluid studies showed normal pressure, dynamics and clear colorless fluid with 4 white blood cells per cubic millimeter and 42 mg. of total protein, 81 mg. of sugar, 718 mg. of chlorides per hundred cubic centimeters, a normal colloidal gold curve and a negative Wassermann reaction.

Special Studies.—Visual acuity was 20/20 bilaterally with normal fundi and visual fields. Roentgenograms of the chest showed normal conditions and our electrocardiogram disclosed sinus tachycardia and slight right axis deviation. Electrical studies (chronaxia measurement) by Dr. Joseph Moldaver showed partial denervation of the deltoid, anconeus, infraspinatus and supraspinatus muscles. On the right side, the deltoid was less affected but the adductor pollicis brevis also showed slight involvement. All other muscles showed normal excitability.

Diagnostic Impression.—It was our impression that the patient had a radiculo-neuropathy involving fibers of fourth, fifth and sixth cervical nerves bilaterally, motor and sensory, left more than right, with minor involvement of the lumbar roots on the left, as a result of smallpox vaccination.

Course of Illness.—The patient was given a high vitamin, high calory and high protein diet with intensive parenteral doses of vitamin B. He was given meperidine hydrochloride (demerol hydrochloride®) for pain, and physical therapy in the form of mild diatheramy through both upper arms and the cervical portion of the spine, reeducation exercises and gentle stretching of the pectoral muscles.

The process had reached its maximum about twenty-four hours previous to the patients admission. Repeated examinations revealed almost daily improvement. The first symptom to appear in the course of the illness, pain, was also the first to decrease and to disappear. Gradually, the muscle status of the patient improved, so that after one month in the hospital only one muscle (the left deltoid) remained graded below "fair" in strength. At the time of discharge, fifty days after admission, there was no pain and the patient was asymptomatic except for some residual

weakness of the deltoid muscle. Four months following discharge he was vastly improved but mild contractures were seen in the pectoral muscles.

Case 2.—*History.*—A 53 year old white Polish-born housewife was revaccinated against smallpox on April 10, 1947, in the region of the left deltoid, with a take in several days followed by pustule and scab formation. Ten days later she began to experience severe, sharp pains in the left shoulder, which after several hours began to radiate down the radial aspect of the left upper extremity to the fingers. This was associated with severe cramping pain in the left shoulder, unrelieved by morphine, and paresthesias in the form of numbness, tingling and "pins and needles" sensations in all fingers and in the left palm. Approximately one to two days after the onset of this syndrome, the patient noted weakness of the left upper extremity. She was unable to raise her arm higher than 90 degrees or to perform precision movements with the fingers of the left hand. During the following two to three weeks the pain, paresthesias and weakness remained stationary. She was admitted to another New York hospital, where a block of the stellate ganglion was performed, with immediate appearance of Horner's syndrome but no change in the pain. After three weeks, there was a slow but definite decrease in the intensity of the pain and paresthesias and in the degree of motor weakness. At this time the patient was admitted to the service of Dr. Henry Alsop Riley at the Neurological Institute of New York. Investigation of the family history revealed twin siblings. A daughter was allergic to dust. The patient's diet had been adequate. There had been no intake of alcohol and no exposure to toxic agents.

Physical Examination.—The patient was a healthy-appearing middle-aged woman in mild distress. Blood pressure, pulse, temperature and respirations were normal. There was a crust 1 cm. in diameter in the left deltoid region. There were occasional fasciculations in the musculature of the left forearm, with definite atrophy in the thenar eminence. There was mild weakness of all muscles of the left upper extremity, more pronounced at the shoulder and less so at the elbow. The deep reflexes were normal and equal with the exception of the left biceps jerk, which was underactive. The superficial reflexes were present, and there were no abnormal reflexes. Sensory examination showed hypesthesia and hypalgesia of the radial aspect of the left upper extremity from shoulder to wrist. The cranial nerves were normal.

Laboratory Examination.—A complete blood count, urinalysis and determinations of nonprotein nitrogen and blood sugar were normal; the Kline test elicited a negative reaction. The sedimentation rate was 30 mm. after one hour. Examination of the spinal fluid showed normal pressure and dynamics, with 2 white cells per cubic millimeter and 27 mg. of total protein per hundred cubic centimeters, a normal colloidal gold curve and a negative Wasserman reaction.

Special Tests.—Electromyograms disclosed no abnormalities. Roentgenograms of the cervical portion of the spine, chest, left shoulder, left hand and right knee showed only moderate osteoarthritic changes. Examination of the eyes revealed normal fundi. Electrical studies (chronaxia measurement) by Dr. Joseph Moldaver indicated no evidence of a lower motor neuron lesion.

Diagnostic Impression.—It was thought that the patient had a radiculoneuropathy involving fibers of the fifth and sixth cervical nerves on the left side, the sensory fibers to a greater degree than the motor. It was believed that the cause was the vaccination against smallpox.

Course of Illness.—The patient was given intensive vitamin B therapy, analgesics and physical therapy in the form of massage, passive and active exercises and

diathermy to the left upper extremity and shoulder. The course had reached its height five days before the patient's admission, and since that time there had been a slow but definite improvement in the pain, paresthesias and motor deficit. The pain and paresthesias improved more rapidly than the motor impairment. By the fifth hospital day, there were no further complaints of pain, and at the time of discharge from the hospital the patient's motor power was practically normal.

CASE 3.—*History.*—A 65 year old white American-born male clerk was revaccinated on April 28, 1947, in the region of the left deltoid, the first successful vaccination having been performed at the age of 12. There was a strongly positive "take" which began after three days, and by the eighth day he had a diffuse, painful, red swelling of the left arm which gradually subsided. On May 8, ten days after vaccination, the patient complained of a sensation "pins and needles" in his left foot, which persisted with little change until the time of admission. On May 11, the same paresthesias appeared in the fingers of both hands and in the right foot. On May 12, weakness of the legs and a tendency to lose his balance developed. The family, personal and past medical histories were not significant. His diet was well balanced, and there was no alcoholism or exposure to toxic agents. There was no history of allergic phenomena in the patient or in his family.

Physical Examination.—The patient was admitted to the service of Dr. Irving Pardee at the Neurological Institute of New York on May 14. He was an elderly well nourished man who had a crust at the insertion of the left deltoid. The blood pressure was 168 systolic and 90 diastolic. Temperature, pulse rate and respiration rate were normal. There was a widened base, staggering and foot drop on the right. The calves were tender but not atrophic. There was definite weakness of the fingers, wrists, elbows and shoulders and of the feet and knees. The right side was more affected than the left throughout. The deep reflexes in the upper extremities were absent, and those in the lower extremities were decreased. The superficial reflexes were not obtainable, and there were no abnormal reflexes. The cranial nerves were normal. Vibration sense was absent in the lower extremities, and there were hypesthesia and hypalgesia bilaterally to midthigh and midarm, more marked distally.

Laboratory Studies.—The Kline reaction, blood sugar level, cephalin flocculation reaction, serum acid phosphatase activity, inorganic phosphorus level, sulfobromophthalein sodium excretion, serum protein level, nonprotein nitrogen level, sedimentation rate, results of urinalysis, blood count and results of gastric anlysis were all normal. The spinal fluid was under normal pressure, contained 4 white blood cells per cubic millimeter and 70 mg. of total protein per hundred cubic centimeters; the colloidal gold curve was normal and the Wassermann reaction negative.

Special Studies.—The electrocardiogram and roentgenograms of the chest, abdomen and skull were normal. Electrical studies (chronaxia measurement) by Dr. Moldaver revealed partial denervation in the muscles of the calves and those supplied by the common peroneal nerves.

Diagnostic Impression.—It was our impression that the patient had a peripheral polyneuropathy of postvaccinal origin.

Course of Illness.—The patient received intensive vitamin B therapy and physical therapy in the form of active exercises. Gradually during his twenty-one day stay in the hospital there was definite improvement in motor strength and

disappearance of the paresthesias. At the time of discharge from the hospital muscle power was good throughout. He was seen in the neurologic division of the Vanderbilt Clinic three weeks after discharge, at which time it was stated that the condition seemed to have cleared up. However, the patient complained on rare occasions of a "little numbness in the hands."

CASE 4.—*History.*—A 39 year old white married American-born clerk was revaccinated in the region of the left deltoid on April 15, 1947, his first successful vaccination having been in childhood. On April 29, he began to experience severe sharp pain in the region of the right infraspinatus muscle, and over a period of two days the pain spread to the entire lateral aspect of his right shoulder. For the next several days, the pain increased. He described it as the severest pain he had ever experienced. It was not relieved by medication. At the height of the pain, he began to feel "numbness and tiredness" of the entire right arm. After a period of seven to ten days the severe pain began to subside gradually, and at this time he noticed that his right shoulder was weak. After several weeks, the motor deficit began to improve, and it was at this time that he was seen in the neurologic division of the Vanderbilt Clinic. There was no personal or family history of allergy. His diet was well balanced; he drank no alcoholic beverages, and there was no exposure to toxic agents. The patient's brother had always been "highly nervous," and a niece had had hemiplegia as a child.

Physical Examination.—The patient was a healthy-appearing man who showed atrophy of both the inferior and the superior spinatus muscle on the right, the inferior being more atrophied than the superior. Lateral rotation and abduction were definitely impaired on the right. The deep reflexes in the right upper extremity were less active than those in the left. The superficial reflexes were present, and there were no abnormal reflexes. No sensory changes were found. The rest of the neurologic examination revealed entirely normal conditions.

Special Studies.—Electrical studies (chronaxia measurement) by Dr. Moldaver showed partial denervation of the right infraspinatus and supraspinatus muscles, the former being involved more than the latter.

Diagnostic Impression.—It was felt that the patient had a radiculopathy involving mainly the fibers of the fifth and sixth cervical nerves on the right, both motor and sensory, making up the suprascapular nerve.

Course of Illness.—The patient was given large amounts of vitamin B with physical therapy and over the course of several months became symptom free.

CASE 5.—*History.*—A 24 year old white male bookkeeper was vaccinated in the left deltoid region during the second week of April 1947, for the second time. A papule and pustule rapidly formed. Within four days the arm became swollen, and there was a mild elevation of temperature. Approximately seven days following the vaccination, the patient began to experience severe pain in the left shoulder. The next day the pain was much less severe but there was difficulty in raising the left arm. At this time he was seen in the neurologic division of the Vandervilt Clinic. There was no history of alcoholic intake, dietary deficiency or exposure to toxic agents. There was no family history of neurologic or psychiatric illness. There was no personal or family history of allergic phenomena.

Physical Examination.—The patient appeared healthy. There was pronounced atrophy of the left shoulder, the deltoid and the infraspinatus muscles being most involved. The scapular reflex was absent on the left, but the other reflexes were normal. There was marked weakness of abduction and internal rotation on the

left. There was decreased sensation for all modalities in a circular area 4 cm. in diameter over the lateral aspect of the left shoulder. The rest of the examination revealed entirely normal conditions.

Special Studies.—Roentgenograms of the left shoulder showed no abnormalties. Electrical studies by Dr. Moldaver disclosed increase of chronaxia of the left deltoid muscle (2.8 seconds, compared with 0.3 second on the unaffected side). Electromyographic studies showed single axon potentials in the left deltoid muscle.

Diagnostic Impressions.—The patient was thought to have postvaccinal neuropathy involving the axillary nerve, and possibly the suprascapular nerve, on the left.

Course of Illness.—The patient received physical therapy and vitamins and improved rapidly, attaining nearly complete clinical recovery after four months.

ANALYSIS OF CASES

An analysis of the 5 cases reveals the following facts: 1. The ages ranged between 35 and 65. 2. Four of the 5 patients were male. 3. In all the reaction followed revaccination for smallpox. 4. The site of inoculation was in the deltoid region. 5. In 2 of the 5 cases there were excessive local inflammatory responses. 6. The site of involvement was independent of the area of inoculation. 7. The incubation period varied from seven to fourteen days. 8. There was a hyperacute onset with severe sharp pain in the shoulder in 4 cases and paresthesias in 1. 9. In 4 cases there was primary involvement of fibers from the fifth and sixth cervical nerves, and in 1 peripheral polyneuropathy. 10. All patients showed marked weakness after one to four days. 11. Systemic complaints were mild to absent. 12. Weakness improved after several weeks. 13. In no case was there a history of alcoholic intake, dietary inadequacy or exposure to toxic agents. 14. All had muscle tenderness, decreased tone, decreased to absent deep reflexes, atrophy and paresis. 15. Four showed objective, and all showed subjective, sensory disturbances. 16. One showed fasciculations. 17. The spinal fluid protein was normal in 4 patients and somewhat elevated in 1. 18. Results of other laboratory studies were essentially normal. 19. Four patients showed denervation by electrical studies. 20. All received vitamin therapy and physical therapy, with good results. 21. All had practically total clinical recovery in four months. 22. Sensory improvement began much earlier than motor improvement and tended to be more nearly complete. 23. As a sequela, 1 patient had mild contractures of the pectoral muscles.

The diagnosis is not difficult if the patients are questioned concerning recent injections or vaccinations. In late summer, one may think of poliomyelitis. However, the lack of significant elevation of temperature or systemic complaints, the absence of cells or other abnormalities in the spinal fluid, the hyperacute onset with intense pain, the presence of objective sensory findings and the distribution of the lower motor

neuron involvement should make the diagnosis clear. In our 5 cases the diagnoses made by the family physicians were "fibrositis," "spinal cord tumor," "subdeltoid bursitis" and "neuritis" (in 2 cases). The erroneous diagnoses can be understood when it is realized that this entity is rare. There have been only 2 papers in English on the subject and no reliable case report of the entity alone.

A history of vaccination against smallpox seven to fourteen days previous to the onset of symptoms is the one most important point in the diagnosis.

REVIEW OF THE LITERATURE

Knoepfelmacher [10] reported the case of a 10 year old child in whom complete paralysis of the right side of the face developed on the eleventh day following vaccination; it gradually improved over a course of weeks. The child lived near Vienna, where an epidemic of poliomyelitis was in progress and on the day before the onset took a hike in the woods and "caught cold." The author felt that both poliomyelitis and ordinary Bell's palsy were to be considered as possible diagnoses in addition to a postvaccinal complication.

Knoepfelmacher [10] also reported the case of a 7 year old child in whom a normal vaccination reaction was accompanied with distressing torticollis. The author interpreted this case also as an instance of postvaccinal neuritis.

De Monchy [11] reported on a 1½ year old child who was found to have atrophy and flaccid paralysis in the distribution of the left ulnar, median and musculocutaneous nerves following vaccination on the left upper arm associated with an intense reaction. There was no evidence of sensory involvement. This author felt that the differential diagnosis rested between neuritis caused by a local diffusion of toxins and an encephalomyelitis involving the anterior horn of that particular region. Largely because the child had begun to show improvement at the end of three months, he felt that the latter was the more likely diagnosis.

Van Bogaert [12] reported a case in which he stated that the differential diagnosis rested between poliomyelitis, postvaccinal neuritis and a peripheral neuritis. After a lengthy discussion, he decided that the last diagnosis was the most plausible.

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10. Knoepfelmacher, W.: Encephalitis postvaccinatoria, Wien. klin. Wchnschr. **43**:97, 1930.

11. De Monchy, S. J. R.: Neuritis postvaccinalis, Nederl. tijdschr. v. geneesk. **74**:755-766, 1930.

12. Van Bogaert, L., and Borremans: Encéphalites vaccinales, poliomyélite et polynévrites survenant dans les jours qui suivent une vaccination; difficulté de ces diagnostics, J. de neurol. et de psychiat. **31**:653-664, 1931.

Harrison [13] reported the case of a 19 year old youth, who, at the age of 3 began having "eye trouble," at which time the serologic tests for syphilis of both the patient and his parents elicited positive reactions. Intensive antisyphilitic therapy was given and the reactions became negative. However, a constant nystagmus and definitely decreased visual acuity persisted. Ten days after vaccination there were malaise, nausea, repeated vomiting and swelling around the eyes. During the next three months, there were intermittent nausea and vomiting, the longest attack lasting one month. During part of this time, the patient was bedridden and unable to retain food. There then developed, three months after vaccination, awkwardness in the extremities followed by marked weakness, progressive atrophy of the extremities, loss of acuity of taste and smell, burning in the palms and legs and pain in the calves and forearms. Examination showed a "strikingly emaciated" youth with a constant rotary nystagmus. In the distal aspect of the extremities there were severe motor deficit, anesthesia and atrophy. Hyperesthesia was found in the remaining parts of the extremities. All reflexes were absent. Results of all laboratory studies, including the Wassermann test, were normal. There was a slow improvement with total recovery in a year. Harrison stated that he was not certain as to the postvaccinal nature of the case, since the clinical picture of postvaccinal neuritis was not known. Furthermore, he was not able to rule out a flaring up of a syphilitic neuritis by the vaccinia virus.

This author discussed both etiologic factors carefully and concluded that "it seems impossible to escape the conclusion that there was an etiological relationship of some sort between the vaccination and the polyneuritis." In reviewing this case, it seems quite likely that the patient had an avitaminosis, and a polyneuropathy as a result of the prolonged vomiting.

Young and Moore [14] reported on a 2½ year old girl, who twenty-seven days after a normal vaccination reaction became irritable, showed lack of interest and became drowsy and anorexic. There began to be pain in the legs and back followed by difficulty in walking. Examination showed pronounced weakness of the lower extremities with bilateral foot drop, slightly decreased tone and absence of deep reflexes, with mild muscle tenderness and hyperesthesia. The upper limbs were only mildly affected. Laboratory studies showed 50 mg. of total protein per hundred cubic centimeters of spinal fluid. Under treatment, the patient improved and in two months was able to walk and in six

13. Harrison, F. F.: Postvaccinal Polyneuritis: Clinical Miscellany, The Mary Imogene Bassett Hospital, Cooperstown, New York, Springfield, Ill., Charles C Thomas, Publisher, 1935, vol. 11, pp. 91-101.

14. Young, R. H., and Moore, C.: Postvaccinal Neuronitis, J. Pediat. **18**:248, 1941.

months was well. It seems quite likely that the patient did have a postvaccinal polyneuropathy, but there also seems to be some evidence of a mild coexistent encephalitis.

PATHOLOGY

Because of the benign course of the postvaccinal neuritides, postmortem findings are not available, either in our experience or in the literature. It must be emphasized at this point that neuritic involvement may occur during the course of postvaccinal encephalitis. There are many cases reported in which there is evidence of involvement of peripheral nerves or roots, in addition to the encephalomyelitic process. Leiner,[15] one of the earlier writers on the subject, described a case of meningoencephalomyelitis following vaccination, which was associated with a unilateral ulnar nerve neuritis. Lamm[16] presented a case which began with neuritic symptoms and signs referable to the left leg in the form of pains, paralysis and absence of deep reflexes, which was followed by typical encephalitis and death.

Because the two entities can occur simultaneously, attention should be given to the pathologic changes in roots and nerves in postvaccinal encephalomyelitis. Because of the more prominent and more serious aspects of the encephalitis, the neuritic involvement is usually overlooked, or at least not emphasized, by both the clinician and the pathologist.[17] There are, therefore, few pathologic studies of encephalitis which describe root and nerve findings.

Perdrau[18] found demyelination in the anterior roots of the ninth thoracic nerve and inflammatory phenomena in the distal end of the brachial plexus in a patient with postvaccinal encephalitis. There was also a mild infiltration of lymphocytes and plasma cells in the spinal ganglia. Swan[19] found that the nerve roots from the medulla showed

15. Leiner, C.: Ueber zerebrale Krankheitserscheinungen, Med. Klin. **22**: (no. 12):441-444, 1926.

16. Lamm, S. S.: Postvaccinal Encephalitis, Am. J. Dis. Child. **56**:824-830 (Oct.) 1938.

17. Hassin, G. B., and Geiger, J. C.: Postvaccinal Encephalitis, Arch. Neurol. & Psychiat. **23**:481-493 (March) 1930. Turnbull, H. M., and McIntosh, J.: Encephalo-Myelitis Following Vaccination, Brit. J. Exper. Path. **7**:181, 1926. McIntosh, J., and Scarff, R. W.: The Histology of Some Virus Infections of the Central Nervous System, Proc. Roy. Soc. Med. **21**:705, 1927. Luksch, F.: Blatternimpfung und Encephalitis, Med. Klin. **20**:1170 (Aug. 24) 1924. Bouman, L., and Bok, S. T.: Die Histopathologie der Encephalitis post vaccinationem, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:495, 1927.

18. Perdrau, J. L.: The Histology of Post-Vaccinal Encephalitis, J. Path. & Bact. **31**:17, 1928.

19. Swan, C.: A Case of Encephalo-Myelitis Following Vaccination, M. J. Australia **1**:152, 1944.

partial demyelination. Lamm [16] observed extensive demyelination in the midthoracic portion of the left phrenic nerve in his patient. No changes were found in the lower cervical ganglia or brachial plexus of either side by Coyle and Hurst [20] in a careful study.

FAMILIAL AND NEUROPATHIC FACTORS

Familial and neuropathic tendencies have been mentioned as predisposing to central nervous system complications of smallpox vaccination. Eckstein,[21] Lucksch,[22] Murano [23] and Burton and Weir [24] stressed the constitutional predisposition which they thought was necessary for the development of these complications. Thomsen [25] also expressed belief in a constitutional factor which was frequently present in cases in which encephalitis developed, and he cited instances of the occurrence of several cases in the same family. These ideas have occasionally been endorsed not only in the postvaccinal disturbances but in many other disorders of the nervous system.

Polyneuritis developed in two sisters and a brother within two weeks after the administration of ether for an operation.[26] An excellent review of the entire subject of the familial and hereditary aspects of nervous diseases can be found in Gates's book.[27]

Closely allied to the concept of familial occurrence of disease is that of the neuropathic constitution, which assumes that certain persons have organ systems that are predisposed to disease. A case has been reported [28] in which meningitis complicated mumps on one occasion, and encephalitis occurred with measles two years later. In the neurologic

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20. Coyle, C. D., and Hurst, E. W.: Acute Disseminated Encephalomyelitis Following Vaccination, Lancet **2**:1246-1428, 1929.

21. Eckstein, A.: Encephalitis im Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **36**:579, 1929.

22. Lucksch, F.: Ueber Enzephalitis nach Varicellae, Variola, nach Vaccination and nach Morbilli, Med. Klin. **28**:1554-1557, 1932.

23. Murano, G.: On a Case of Postvaccinic Meningo-Encephalitis, Pediatria **45**:714, 1937.

24. Burton, A. H. G., and Weir, H. G.: Postvaccinal and Measles Encephalomyelitis, Report on Two Cases Which Recovered, Lancet **2**:561-562, 1941.

25. Thomsen, O.: Akute nicht suppuartive Entzündungen im Zentral Nervensystem, Acta path. et microbiol. Scandinav. **9**:407, 1932.

26. Hammes, E. M., and Frary, L. G.: Polyneuritis Associated with Ether Anesthesia Occuring in Three Members of One Family, Arch. Neurol. & Psychiat. **35**:617-628 (March) 1936.

27. Gates, R.: Human Genetics, New York, The Macmillan Company, 1946, pp. 955-1086.

28. Bridgeman, M. L.: Meningitis Complicating Mumps and Encephalitis Complicating Measles in the Same Child, Am. J. Dis. Child. **53**:804 (March) 1937.

clinic of this Institute we have recently seen several patients, who, many years before the onset of spontaneous demyelinating disease, had transient episodes of neuritis or myelitis following prophylactic immunizations.

If an attempt is made to analyze the cases reported in this paper, it is seen that 2 of the patients had twin siblings. A brother of one had died with convulsions in childhood. Another patient's niece had hemiplegia as a child. One of the patients had a "nervous breakdown" and a duodenal ulcer. No information was available concerning the family history of the fifth patient.

In summary, it may be said that there seems to be evidence that certain individuals or families have an increased susceptibility to the development of certain diseases of the nervous system, both primary and secondary to other processes.

ROLE OF RESISTANCE

It is agreed that many disease processes are directly related to the resistance of the person. The infections provide the best example, and here can be found species, racial and inherited factors. Age, climate, fatigue, nutrition and generalized physiologic well-being are all important. These factors are also observed in other diseases. It is well known that cutaneous lesions definitely predispose the vaccinated person to various dermatologic complications. Generalized vaccinia is more likely to occur in persons who have chronic cutaneous disorders, such as atopic eczema, eczematoid dermatitis, impetigo and intertrigo. Furthermore, the severer the cutaneous disorder, the severer the generalized vaccinia. Many authors have mentioned cases of encephalitis occuring in persons who had had an infection at the time of vaccination. Coyle and Hurst [20] reported 2 cases, in 1 of which the patient had pneumonia and in the other severe furunculosis. Fyfe and Fleming [29] found that most of the patients with postvaccinal encephalitis showed evidence of acute infections of the upper respiratory tract or the generalized infectious processes. No conclusions can be drawn from the cases reported here.

COMMENT

The subject of postvaccinal peripheral nerve and root disturbances may be discussed from several points of view. The subjects to be considered individually are the relations between the postvaccinal neuritides and (1) the postvaccinal encephalomyelitides and (2) the serum neuritides.

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29. Fyfe, G. M., and Fleming, J. B.: Encephalomyelitis Following Vaccination in Fife, Brit. M. J. **2**:671, 1943.

Ford [30] has defined serum neuritis as "neurological symptoms, usually of the spinal nerve roots or peripheral nerves, following the injections of sera for therapeutic purposes or less commonly for the purpose of producing immunity." Up to 1942 Stoldt [31] found 180 reported cases of neuritis after use of tetanus antitoxin, diphtheria antitoxin, streptococcus antitoxin, pneumococcus antitoxin, scarlet fever streptococcus antitoxin, Staphylococcus aureus vaccine and typhoid and paratyphoid vaccines. Robertson and Varmus [32] found over half of the cases to be due to tetanus antitoxin. Allen [33] divided the cases of nervous system complications from serum into four groups: radicular, neuritic, polyneuritic and cerebral. It can be seen from the cases reported in this paper and from the literature that the complications of vaccination also embrace all these types.

The serum neuritides are today believed by most observers [34] to be on the basis of an antigen-antibody interaction. I believe that the postvaccinal neuritides have a similar pathogenesis. The clinical features common to the serum neuritides and postvaccinal neuritides include the following: (1) incubation period most commonly seven to fourteen days; (2) frequently severe reaction at the site of injection; (3) hyperacute onset; (4) rapid attainment of maximum intensity; (5) involvement independent of the site of inoculation; (6) intense neuritic pain the first manifestation; (7) process most commonly in arms or shoulders (muscles innervated by the fifth and sixth cervical nerve) but in some

30. Ford, F. R.: Diseases of the Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1946, p. 728.

31. Stoldt, J.: Ueber die Serumpolyneuritis, Arch. f. Kinderh. **127–129**:133, 1942.

32. Robertson, H. F., and Varmus, F.: Report of a Case of Peripheral Neuritis with Hypertension Following Serum Therapy, Mil. Surgeon **95**:129-132, 1944.

33. Allen, I. M.: Neurological Complications of Serum Treatment with Report of a Case, Lancet **2**:1128-1131, 1931.

34. (*a*) Mason, V. R.: Optic Neuritis in Serum Sickness, J. A. M. A. **78**:88 (Jan. 14) 1922. (*b*) Wilson, G., and Hadden, S. B: Neuritis and Multiple Neuritis Following Serum Therapy, ibid. **98**:123 (Jan. 9) 1932. (*c*) Doyle, J. B.: Neurologic Complications of Serum Sickness, Am. J. M. Sc. **185**:484, 1933. (*d*) Stolt, J.: Ueber die Serumpolyneuritis, Arch. f. Kinderh. **127**:129-133, 1942. (*e*) Karnosh, L., and Zucker, E. M.: Horse Serum Neuritis, Ohio State M. J. **39**:416-417, 1943. (*f*) Bennett, A. E.: Horse Serum Neuritis, with Report of Five Cases, J. A. M. A. **112**:590-596 (Feb. 18) 1939. (*g*) Kraus, W. M., and Chaney, L. B.: Serum Disease of Nervous System: Report of Three Cases, Arch. Neurol. & Psychiat. **37**:1036-1047 (May) 1937. (*h*) Kennedy, F.: Allergic Reactions in Nervous System, Tr. Am. Neurol. A. **61**:49-51, 1935. (*i*) Kennedy, F.: Allergic Manifestation in Nervous System, New York State J. Med. **36**: 469-474, 1936. (*j*) Young, F.: Peripheral Nerve Paralysis Following Use of Various Serums: Report of Case and Review of Literature, J. A. M. A. **98**:1139-1143 (April 2) 1932.

cases peripheral; (8) paresis or paralysis within a few days followed rapidly by atrophy; (9) alteration of the electrical reaction; (10) tenderness of nerve trunks and muscles; (11) absence of deep reflexes; (12) sensory changes often present but involvement predominantly motor; (13) essentially normal results of laboratory studies, and (14) rapid improvement with practically total clinical recovery in several months.

In the serum neuritides, however, there may be symptoms of serum sickness, such as fever, urticaria, angioneurotic edema, articular pains, eosinophilia, headache and vomiting. The absence of the symptoms of serum sickness in the postvaccinal neuritides does not detract from the similarity between the two entities. First, it has been found that a greater incidence of serum sickness occurs when larger quantities of serum are used, and it has been shown that it is the amount [35] rather than any refinement [36] of the serum which had to do with the reaction obtained. Secondly, the frequency of serum disease is much less after cutaneous administration than after intravenous injection [35b] and, thirdly, it is thought that the incidence of serum sickness is greater when very fresh serum is used.[35a] Furthermore, it has been shown that serum sickness occurs in only approximately one quarter of the cases.[34j] Therefore the absence of serum sickness from the postvaccinal nervous system complications does not detract from the probable relationship between the two entities, since the amount of lymph absorbed is very small, is by no means fresh and is not injected intravenously. The superficial scarification carried out in smallpox vaccination probably promotes antigenic activity.

There is apparently a relationship between the group of serum neuritides and localized neuritis of the shoulder girdle as reported by Burnard and Fox [38] and Spillane.[39] In this syndrome, too, there is acute onset of sharp pain about the affected shoulder followed in several

35. (*a*) Coca, A. F.: Deigert, G., and Menger, E. F.; cited by Black, J. H.: Hypersensitiveness, in Tice, F.: Practice of Medicine, vol. 1, Hagerstown, Md., W. F. Prior Company, 1924. (*b*) Woltman, H. W.: Neuritis and Other Diseases or Injuries of Peripheral Nerves, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1924, vol. 9, p. 387.

36. Hunt, L. W.: Recent Observations in Serum Disease, J. A. M. A. **99**:909-912 (Sept. 10) 1932.

37. Black, J. H.: Hypersensitiveness, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1924, vol. 1, p. 139.

38. Burnard, E. D., and Fox, T. G.: Multiple Neuritis of Shoulder Girdle: Report of Nine Cases Occurring in Second New Zealand Expeditionary Force, New Zealand M. J. **41**:243-247, 1942.

39. Spillane, J. D.: Localized Neuritis of Shoulder Girdle: Report of Forty-six Cases in MEF, Lancet **2**:532-535, 1943.

days by muscular weakness and considerable atrophy with no changes in the spinal fluid. This condition could not be traced to any injection. Eighteen cases have been reported by Weinstein,[40] who found that all his patients had received typhoid or typhus vaccine one to twelve weeks prior to the onset of illness. He stated that he considers this entity identical with serum neuritis and believes that the cause is a vascular sensitivity provoked by prophylactic injections of vaccine. The bases for his belief are as follows: (1) the apoplectiform onset; (2) the fact that the paralysis was initially maximal; (3) the localized nature of the paralysis, suggestive of some sort of vascular process, and (4) the fact that a neuropathy may develop after injection of foreign protein incriminates allergic phenomena. Weinstein also pointed out that a similarity is seen in the neuropathy which occurs with periarteritis nodosa.

Multiple neuritis has been reported occurring with or following sulfonamide therapy. Blankenhorn [41] found it in 6 of 627 patients. Müller [42] reported 7 cases. Kolb and Gray [43] reported 7 cases of localized peripheral neuritis complicating penicillin therapy. Peripheral nerve disturbances following sulfonamides and penicillin are tied more closely to the postserum and postvaccinal neuropathies by the work of Gordon,[44] who described serum sickness due to penicillin and by the work of Longcope,[45] who described serum sickness from sulfonamides, and other drugs. McLure [46] and Davidson [47] and Davis have shown that various allergic reactions, such as urticaria, occasionally occur in association with the nervous system complications of smallpox vaccination.

Some authors, including Ford,[30] have attempted to differentiate between the neuritides following vaccination or use of serums by dividing them into two groups, of which one is and the other is not associated

40. Weinstein, E. A.: Localized Nontraumatic Neuropathy in Military Personnel, Arch. Neurol. & Psychiat. **57**:369-376 (March) 1947.

41. Blankenhorn, M. A.: Multiple Peripheral Neuritis Occurring with Sulfonamide Therapy, Ann. Int. Med. **20**:423-430, 1944.

42. Müller, R.: Polyneuritis Following Sulfonamide Therapy, Acta med. Scandinav. **121**:95-113, 1945.

43. Kolb, L. C., and Gray, S. J.: Peripheral Neuritis as a Complication of Penicillin Therapy, J. A. M. A. **132**:323-326 (Oct. 12) 1946.

44. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, J. A. M. A. **131**:727-730 (June 29) 1946.

45. Longcope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, Medicine **22**:251-286, 1943.

46. McLure, W. B.: Urticaria and Nervous Manifestations Following Revaccination, China M. J. **44**:526-531, 1930.

47. Davidson, L. S. P., and David, L. J.: Generalized Vaccine Reactions in Allergic Subjects, Lancet **2**:103-104, 1943.

with allergic phenomena. This grouping is probably artificial, for there are too many other factors concerned, as stressed previously, including amount of serum or vaccine, method of inoculation, freshness of serum, types of contained proteins, types and viability of bacteria or viruses and individual susceptibility of the patient.

The only difference among the nervous system complications due to vaccination, serum, sulfonamides, penicillin and other drugs is the sensitizing substance. The nervous system component which is rendered antigenic, its formation of antibodies and their interaction are probably identical in all these allergic neuritides.

It should be stated at this point that it is not definitely known whether it is the vaccinia virus or the calf lymph that is the offending agent in smallpox vaccine, even though the latter theory is rarely suggested. The striking similarity between this postvaccinal syndrome and the serum neuritides may point to the calf lymph as the offending agent.

The postvaccinal neuritides may also be thought of as being related to the postvaccinal encephalomyelitides. As previously stressed, root and nerve disturbances may occur simultaneously with the encephalomyelitic complication of smallpox vaccination. The question then arises, what is the relation between these two entities? They have many features in common, the most important of which are the fairly constant incubation period and the sudden onset. It is true, however, that the encephalitic complication occurs predominantly in a certain age group—namely, 3 to 9 years—and predominantly after primary vaccination. This is not in keeping with the picture of postvaccinal neuritis. It is difficult to explain these two important differences with our present knowledge.

It is my opinion that both the postvaccinal neuritides and the encephalomyelitides may be classified as allergic in nature. In the latter, it is thought that a fraction of the vaccine acts on or combines with a component of the nervous system, possibly in the white matter,[48] rendering this substance antigenic. Antibodies are then formed, which, on reaching a certain titer, act with the shock tissue to produce the lesions. However, the exact mechanism in the case of the neuritides must of necessity be somewhat different, because of the age difference, because they occur so rarely together, because encephalitis occurs so predominantly after primary vaccination and because of the different anatomic foci of involvement. This difference probably lies in the

48. Kabat, E. A.; Wolf, A., and Bezer, A. E.: The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants, J. Exper. Med. **85**:117-130, 1947.

fact that the neuritis is caused by a different allergic phenomenon—edema in and around the root and nerve rather than a demyelinating process—just as there may be urticaria and rhinitis or dermatitis and asthma in the same person. Here it may be added that while the pathologic changes in the postvaccinal neuritides are unknown, as previously stated, tissue from patients who have serum neuropathy has shown engorgement of the vessels, hemorrhagic exudates and edema in both the central [49] and peripheral nervous systems.

The recent experimental work by Kabat, Wolf and Bezer,[48] Morgan [50] and Morrison [51] tends to support these ideas. Both of these groups of workers showed that a disease process very similar to disseminated encephalomyelitis can be produced in monkeys by the injections of emulsions of rabbit or monkey brain which they hypothesize involves the formation of antibodies to the injected brain tissue, which then react with the antigen in the central nervous system of the animal to produce the disease. Kabat, Wolf and Bezer [48] have expressed the belief that an antigen-antibody union in the perivascular tissue either directly or indirectly gives rise to the inflammatory reaction and degeneration both in the vessel wall and in the surrounding tissue. It is important to note, however, that no lesions were found in the peripheral nerves, either when brain and spinal cord were used as the antigen or when peripheral nerve itself was used. This work, plus the rare occurrence of peripheral nerve symptoms, signs or marked pathologic changes in all the demyelinating diseases, may indicate that either peripheral nerve acts very poorly to induce antigenic responses, with the result that when changes do follow they are of the nature of engorgement of vessels, hemorrhagic exudates and edema and not demyelination or sensitization of a different component of the tissue. Therefore, the underlying etiologic factor appears to be the same in the postvaccinal nervous system complications as in the serum neuritides, although the exact pathogenesis probably differs, as stated.

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49. Roger, H.; Poursines, Y., and Recorder, M.: Polynévrite après sérothérapie antitétanique curative, avec participation du névraxe et des méninges (observations anatomoclinique), Rev. neurol. **1**:1078, 1934. Cathala, J.; Garcin, R.; Gabriel, P., and Laplace, R.: Réitération spontanée de la paralysie post-sérothérapique; syndrome radiculonévritique et urticaire evoluant conjointement poussées après sérotherapy auto-scarlatineuse, Presse méd. **52**: 1934.

50. Morgan, I. M.: Allergic Encephalomyelitis in Monkeys in Response to Injections of Normal Monkey Nervous Tissue, J. Exper. Med. **85**:131-140, 1947.

51. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:931-416 (Oct.) 1947.

SUMMARY

Five cases of disturbances of peripheral nerves and roots following smallpox vaccination are presented and the clinical characteristics. The literature on the subject is reviewed. The entity is described from the aspects of its clinical picture, possible pathogenesis, role of familial or neuropathic tendencies, role of resistance and relation to other neurologic diseases, such as postvaccinal encephalomyelitis, serum neuritis and neuritides following the administration of many drugs.

CONCLUSIONS

1. Postvaccinal disturbances of both peripheral nerves and of roots occur after a relatively constant incubation period.

2. The entity is rare. No clearcut case of postvaccinal disturbance of peripheral nerves or roots alone has been reported.

3. A typical clinical picture occurs, and the prognosis is good.

4. There may be motor, sensory or mixed involvement. The sensory disturbance (pain) initiates the disease, producing marked distress, and causes the patient to seek medical advice. This is rapidly followed by motor impairment, which tends to be more extensive and longer lasting than the sensory.

5. Efficient physical therapy must be carried out in order to prevent sequelae such as contractures.

6. Neuritic involvement may occur as part of the clinical picture of the postvaccinal encephalomyelitides.

7. It is thought that the postvaccinal disturbances of peripheral nerves and roots, belong in the same group as the serum neuritides.

8. The postvaccinal neuritides seem also to be related to neuritides associated with sulfonamide and penicillin therapy and perhaps with periarteritis nodosa, in all of which allergy plays an important role.

9. Finally, while the incidence of the infectious diseases, which are common, depends on the virulence of the organism and the susceptibility of the host, the complications of vaccination, which are not at all common, probably depend on a vastly more complicated mechanism, involving (*a*) a constitutional factor, (*b*) the existence of a good antibody formation mechanism which in itself is partly constitutional, (*c*) an ill defined lack of resistance either generalized or organ specific and (*d*) the entry of the exciting agent into the body—in this case, the vaccinia vaccine.

MULTIPLE METASTATIC ABSCESSES OF THE BRAIN

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ACCORDING to Dandy,[1] "one can hardly expect to cure multiple abscesses by surgical means unless they are contiguous and limited to two or three in number." Kahn [2] stated that metastatic abscesses are due to either pleuropulmonary infections or generalized pyemia, that they are usually due to anaerobic organisms and do not encapsulate and that in his hands the outcome has invariably been fatal. Coleman [3] wrote that metastatic abscesses rarely yield to surgical treatment because of the serious systemic infection preceding their development and the multiplicity of the lesions. King [4] stated, "It is granted that there is no likelihood of recovery following operation in cases of multiple abscesses of the brain." These statements were for the most part made prior to the advent of chemotherapy and the use of antibiotics. In 1946, I [5] reported my early experiences with penicillin in the treatment of brain abscess and cited 1 case with two contiguous abscesses secondary to pleuropulmonary infection in a patient who recovered and returned to active duty in the United States Marine Corps. Grant [6] in 1943 reported the case of a 33 year old man who had multiple abscesses secondary to empyema. Sulfathiazole was used as a chemotherapeutic agent, and the abscesses were drained by aspiration. The brain was needled at least thirty times, and on five occasions pus was recovered. All these abscesses were in the right cerebral hemisphere; so they were probably contiguous. Tolosa,[7] in

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From the Department of Neurosurgery, Washington University Medical School, and the St. Louis Children's Hospital.

1. Dandy, W. E.: Infections of Brain, Meninges and Skull, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 12, p. 380.

2. Kahn, E. A.: Brain Abscess: Surgical Treatment, in Bancroft, F. W., and Pilcher, C.: The Nervous System, Philadelphia, J. B. Lippincott Company, 1946, vol. 5, pp. 75-76.

3. Coleman, C. C.: Reduction of Mortality of Brain Abscess by Simple Methods of Treatment, South. M. J. **23**:484, 1930.

4. King, J. E. J.: Acute Metastatic Brain Abscess, South. Surgeon **5**:407, 1936.

5. Furlow, L. T.: Penicillin as an Adjunct to Surgery in the Treatment of Brain Abscess, South. M. J. **38**:312, 1945.

6. Grant, W. T.: Multiple Metastatic Abscesses of the Brain with Recovery, Bull. Los Angeles Neurol. Soc. **8**:89, 1943.

7. Tolosa, E.: Absceso cerebral múltiple, Rev. clin. españ. **21**:16, 1946.

a recent paper, stated that in a series of 30 cases of intracranial abscesses, 4 cases of multiple abscesses were encountered. However, he reported the details of only 2, one secondary to otitis media and the other post-traumatic. Grant,[8] in his excellent review of the literature on the subject of brain abscesses, outlined the sources which cause these lesions, and cited statistics to show that approximately 50 per cent of metastatic abscesses are solitary. While it is a recognized fact that most metastatic abscesses are secondary to pleuropulmonary infections, they can occur as a result of pyemia from any source, and in some instances the cause is never determined. Four such cases were reported by Yaskin, Grant and Groff[9]; all the patients recovered after operation.

In reviewing the subject of brain abscess, one is impressed by the fact that no single method of treatment has been accepted. Since the days of Macewen,[10] important contributions have been made by many neurosurgeons, but most of these reports have expressed concern over the failure to obtain satisfactory results. Vincent[11] and associates in 1937 advocated complete removal of encapsulated abscesses, insisting that sufficient time be allowed for encapsulation but advocating the turning of a bone flap as an initial procedure. Through a small dural opening, exploration with a cannula is carried out, and if the capsule is thick the abscess is dissected out. If, however, the capsule is thin and easily penetrated only aspiration is done; the flap is replaced, but only the scalp is sutured, it being felt that increased intracranial pressure will be taken care of by elevation of the flap. Subsequently, when symptoms recur the abscess is removed *en masse*.

Sachs[12] has expressed the opinion that the ideal method of treatment of brain abscess is complete removal whenever possible. LeBeau[13] has recently reported his further experience with Vincent's method and stated that penicillin has made it possible to treat abscesses as if they were infiltrating gliomas—i. e., if they are in the acute state without encapsulation, a flap is reflected and the area of infection

8. Grant, F. C.: Brain Abscess, Collect. Rev. Internat. Abstr. Surg. **72**:118, 1941.

9. Yaskin, J. C.; Grant, F. C. and Groff, R. A.: Brain Abscess of Undetermined Etiology, Ann. Surg. **107**:492, 1938.

10. Macewen, W.: Pyogenic Infective Diseases of the Brain and Spinal Cord, New York, Glasgow McMillan & Company, 1893.

11. Vincent, M. C.: Le traitement des abcès subaigus et chroniques des hémisphères, Mém. Acad. de chir. **64**:661, 1938. Vincent, C.; David, M., and Askenasy, H.: Sur une méthode de traitement des abcès subaigus et chroniques des hémisphères, cérébraux, Rev. neurol. **49**:1, 1937.

12. Sachs, E.: An Analysis of Brain Abscesses Observed During the Past Thirty Years, Ann. Surg. **123**:785, 1946.

13. LeBeau, J.: Radical Surgery and Penicillin in Brain Abscess, J. Neurosurg. **3**:359, 1946.

together with the contiguous zone of edematous white matter removed; if the abscess is encapsulated, every vestige of the abscess is taken out. He reported 17 such cases; 3 patients operated on prior to the use of penicillin died, whereas of the 14 treated since the use of penicillin 13 recovered. Several months before LeBeau's report, Fincher [14] advocated complete removal whenever possible and stressed the fact that chemotherapy and antibiotics made this a procedure of great practical value.

The following case report shows that even multiple metastatic abscesses may be successfully treated in this manner.

REPORT OF A CASE

J. C. T., a white boy aged 7 years, was admitted to St. Louis Children's Hospital on Aug. 24, 1947, having been referred by Dr. John C. Faris, of Jonesboro, Ark., because of left-sided convulsions, headache and vomiting. The family history revealed nothing of significance except that the father had a congenital dislocation of the left hip, and the past history was entirely noncontributory.

The present illness began about August 1 with an acute episode characterized by anorexia, cough, fever and a red throat. The boy was seen by a local physician, who made a diagnosis of "malarial tonsillitis," but the nature of treatment given is not known. The acute phase of this illness lasted approximately ten days, and at the end of that time he seemed completely recovered and was able to resume his normal activities. However, on August 18, while he was playing in the yard near his home, his mother heard him scream, rushed out and found him having a left-sided convulsion, which involved the face, arm and leg. He was not unconscious. He was taken by car to a hospital in Jonesboro, Ark., where he had numerous seizures, all of which seemed to begin in the left arm and were for the most part confined to the left side but occasionally involved the right arm and right leg to a minor degree. On the next day he was unconscious for approximately seven hours, but it could not be definitely determined whether this was due to the illness or to the medication which he had received in an effort to control his convulsions. On August 21 a lumbar puncture was done. This showed "high pressure," but cytologic studies are not available. Since this procedure he had complained of severe headache and had vomited all food and fluids which he had taken by mouth and so he was transported to St. Louis.

Examination at the time of his admission revealed a markedly dehydrated youngster who was stuporous but who could be aroused. His orientation was poor, and he remembered practically none of the details of his present illness. The left pupil was larger than the right. The fundi showed swelling of the nasal margins of both disks, with a few punctate hemorrhages, more numerous in the right eye. The deep reflexes on the left were hyperactive, but there were no pathologic reflexes. His gait was not tested, but there was no ataxia or dysdiadokokinesis and he had no astereognosis. Roentgenograms of the skull were considered to show no abnormalities. Results of all laboratory studies were within normal limits except for a total leukocyte count of 13,250, with 3 per cent juvenile forms, 6 per cent stab cells, 78 segmented cells and 17 per cent lymphocytes. Hydration was restored by intravenous and subcutaneous admin-

14. Fincher, E. F.: Craniotomy and Total Dissection as a Method in the Treatment of Abscess of the Brain, Ann. Surg. **123**:739, 1946.

istration of fluids, and on August 27 ventriculography was performed. Both ventricles were very small, and the left ventricle, although larger than the right, was displaced to the right and the anterior horn compressed. A note was made which stated that "these films indicate a lesion of the left frontal lobe, but because of the compression and small size of the right ventricle more than one lesion may be present." Immediately after ventriculography a left frontal bone flap was reflected, and the dura was so tight that a lumbar puncture had to be done before it could be opened. About a third of the way back from the tip of the frontal lobe in its midportion was a soft area, and when a needle was inserted at this point pus was encountered at a depth of 1 cm. The needle was left in to prevent leakage, while the surrounding cortex was covered with cottonoid® soaked in penicillin solution. The needle tract was then coagulated and the needle withdrawn. The abscess was uncapped, the capsule picked up and complete enucleation done by finger dissection. The capsule ruptured at one point, but the pus was quickly aspirated. On removal of the abscess capsule the cavity was filled with gelfoam® (oxidizable cellulose gauze) which had been soaked in penicillin. The usual layer closure was done without drainage. Spinal fluid which had been obtained for study showed 110 white cells, and culture of the pus yielded an organism reported as Staphylococcus aureus, but the bacteriologic department felt that this was probably a contaminant.

The child's postoperative course was relatively uneventful. There was an immediate rise in temperature, but under intensive systemic penicillin therapy this quickly subsided, and on September 9 the boy was discharged from the hospital. He was not, however, allowed to return to his home, because there was still a definite suspicion of a second lesion.

He was seen on September 12, when, according to his mother, he had been vomiting at intervals for two days. The bone flap was solid, but there were weakness of his left sixth nerve and definite swelling of both optic disks. He was sent back into the hospital on the same day. The leukocyte count was 12,050, with a slight shift to the left in the differential count.

On September 16 ventriculography was again performed. The needle was first inserted on the right side, but this ventricle was compressed and fluid could not be obtained. The needle was then inserted into the left ventricle and 15 cc. of fluid removed and a like amount of air injected. Roentgenograms showed that this air was all in the left ventricle and that this ventricle was displaced away from the midline, but the configuration of the anterior horn was normal. The needle was reinserted on the right side, and when it was directed slightly upward and forward an abscess was encountered at a depth of about 3 cm.; 50 cc. of thick greenish pus was allowed to flow out through the needle. The abscess cavity was irrigated thoroughly with penicillin in Ringer's solution, and 15,000 units of penicillin together with about 2 cc. of air was left in the abscess cavity. Roentgenograms were then made to determine the exact location of the abscess so that it could be completely removed at a future date. Cultures of this pus were reported as yielding a microaerophilic gamma streptococcus. Cultures made after irrigations with penicillin were sterile. The child's condition improved immediately. He was able to ingest larger quantities of food and fluids without vomiting, but there was little change in the sixth nerve paralysis.

On September 24 the abscess was again aspirated, but only about 3 cc. of pus could be obtained. After cultures had been taken, which proved sterile, the abscess was irrigated with penicillin solution and 10,000 units of penicillin left in. Roentgenograms showed the abscess cavity to be much smaller, and the child's condition remained excellent. The left frontal bone flap, however, was somewhat elevated,

and the papilledema and sixth nerve paralysis remained unchanged. He was discharged on October 10 and was seen in the office on October 17. At that time there had been a definite decrease in the amount of swelling in each fundus and the sixth nerve paralysis was less evident than at the time of his discharge.

This improvement, however, was of short duration. Because of headache and vomiting which had lasted about thirty-six hours, the boy was readmitted to the hospital on October 24. At that time the bone flap was more elevated, and there had been an increase in the amount of swelling in each fundus. The deep reflexes on the left were still more active than those on the right, but there was no weakness of any of the extremities.

On the next day ventriculography was again performed, but it was possible to get air only into the left ventricle. The ventriculograms showed that the left ventricle and the third ventricle were displaced to the left side, indicating a space-occupying lesion on the right. Craniotomy was done immediately, the idea being to enucleate the abscess in the right parietal lobe. A bone flap was reflected and the right ventricle was punctured anteriorly so that the dura could be opened. When the needle was inserted, the abscess capsule could be felt but pus could not be aspirated. The cortex was herniating; hence an incision was rapidly made down to the abscess capsule, and with suction and traction the mass of inflammatory tissue, which was about the size of a golf ball, was enucleated. The wound was then closed tightly without drainage, penicillin being used to irrigate the cavity which was left after the removal of the abscess capsule. A section of the tissue removed showed it to be a thick wall of an abscess with a few drops of liquid pus in the center. After this procedure the child showed a marked personality change. Whereas he had previously been quite independent and able to make friends readily in the ward, he now wanted his mother to be with him constantly, insisted that she feed him and on November 3 became noisy and irrational. The left frontal bone flap continued to be elevated.

On November 4 air was again injected and about 30 cc. of fluid removed from the left ventricle and replaced with air. There was marked displacement of the left ventricle and of the third ventricle to the left side, with no air in the right ventricle. Attempts to hit the right ventricle were unsuccessful, and finally at a depth of 7 cm. in a lateral direction in the anterior portion of the parietal lobe an abscess was entered and 75 cc. of thin pus evacuated. Roentgenograms made after the abscess had been aspirated showed that some of the air had gone across into the right ventricle. There was still displacement of the ventricle toward the left side. The child remained irritable, and the left frontal flap was still elevated, so 40 cc. of thick greenish yellow pus was again aspirated from the abscess cavity on November 8. After the abscess had been flushed out with penicillin solution and 20,000 units injected into the abscess, 6 cc. of air was injected and roentgenograms were made; these showed that the abscess was superficial in the right temporal lobe.

On November 15 a straight incision was made in the temporal region on the right side, extending up to connect with the anterior limb of the flap which had been previously reflected. Enough bone was removed to make a moderate subtemporal decompression, and the dura was reflected in a cruciate manner. An air injection needle was inserted into the midportion of the first temporal convolution, and 30 cc. of thick yellowish pus was aspirated. This reduced the pressure so that an incision could be made through the first temporal convolution down to the abscess capsule, and again, after the surrounding cortex was protected with cottonoid® soaked in penicillin solution, the abscess capsule was completely dissected out. The capsule extended beneath the fissure of Sylvius, deep into

the parietal lobe. The child's postoperative course following this procedure was one of rapid improvement. He was discharged from the hospital on November 26, no longer having choked disks or sixth nerve paralysis. There was, however, on gross testing an incomplete left homonymous hemianopsia, and there had been some weakness and awkwardness of the left arm and leg since the removal of the second abscess, in the parietal lobe.

The patient has been seen on several occasions following operation, the last time being Jan. 3, 1948. At that time he had no complaints, he was able to be up and around without any difficulty, but his mother had noticed that he occasionally would be uncertain of vision on his left side. There was some disturbance of position sense in his left hand, but he used the extremity well and had no astereognosis. His gait was normal. In a report by letter on May 25, 1948, it was stated that he had remained well and that his residual neurologic signs had shown marked regression.

COMMENT

Only two cultures yielded organisms: the first, an organism reported as Staph. aureus, and the second, a microaerophilic gamma streptococcus. The bacteriologic laboratory considered the staphylococcus as a probable contaminant, for it grew out in great profusion in twenty-four hours, the culture then being discarded. The gamma streptococcus, subsequently grown from the second abscess, was apparent only after seventy-two hours' incubation and was probably the organism involved in the pyemic process. Cultures were routinely taken after the abscess had been flushed out with penicillin solution, and these were consistently sterile under all conditions. To me, this seems important and emphasizes the beneficial effect of penicillin, which may be used locally and systemically.

The removal of the abscess in the parietal lobe was probably unnecessary and unwise, though it still contained liquid pus in small amounts. However, because of the failure to visualize the right ventricle, it was assumed that this abscess was responsible for the compression, whereas the abscess in the parietotemporal area was almost certainly the compressing lesion.

In my opinion, repeated aspirations would not have been as effective as enucleation, and it is my firm conviction that intensive chemotherapy to promote localization followed by total removal constitutes the method of treatment most likely to succeed with brain abscesses, whether single or multiple.

RECURRENT HYPERTENSIVE CEREBRAL THROMBOSIS

Clinicopathologic Analysis of Six Cases with Discussion of Pathogenesis

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SINCE Goldblatt's [1] famous experiments on dogs resulting in the production of permanent hypertension similar to hypertensive cardiovascular disease in man, attention has been focused more or less constantly on the kidneys as one of the most important sources of the disease. The role of the brain has received scant attention perhaps because it has been assumed that the cerebral lesions in hypertensive cardiovascular disease were secondary to those in the kidneys.

There is a certain group of patients with hypertension whose chief symptoms are cerebral and in whom evidence of renal involvement may develop only late in the disease. In general, the nature of the illness is not recognized or is incorrectly diagnosed because of the variability of the presenting symptoms. According to Alvarez,[2] it is a specific syndrome which is not found described to any extent in the books or journals and which is seldom discussed at medical meetings. Yet, as he puts it, "One of the commonest diseases of man is a slow petering out toward the end of life and one of the commonest ways of petering out is that of repeated thrombosis of small sclerotic cerebral blood vessels."

An editorial comment on this problem in *The Journal of the American Medical Association* [3] points out the need of close correlation of the clinical phenomena with the results of morphologic studies of the cerebral lesions. Perhaps just as important is the need for uniformity in terminology. In many of the textbooks, little or no mention at all is made of the syndrome. It is variously reported in the literature as

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From the State Hospital for Mental Diseases, Howard, R. I.

1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347-379 (March) 1934.

2. Alvarez, C.: Cerebral Arteriosclerosis with Small Commonly Unrecognized Apoplexies, Geriatrics **1**:189-216 (May) 1946.

3. Recurrent Cerebral Thrombosis as a Nosologic Entity, editorial, J. A. M. A. **131**:940 (March 29) 1946.

"hypertensive encephalopathy" (Oppenheimer and Fishberg,[4] Keith, Wagener and Kernohan,[5] Barship,[6] and Davison and Brill [7]), "hypertensive cerebral attack" (McAlpine [8]), "cerebral crisis" (Campbell and Davies [9]), "chronic hypertension of nervous origin" (Izquierdo [10]), "hypertensive disease of the brain" (Fortune [11] and Scheinker [12]), "hypertensive apoplexy" (Chase [13]), "cerebral form of arterial hypertension" (Thiebault [14]) and "cerebral thromboangiitis obliterans" (Scheinker [15]).

Historically the term "hypertensive encephalopathy" has priority over the others. It was first used by Oppenheimer and Fishberg [4] in 1928 to designate the form of hypertensive cardiovascular disease in which the outstanding manifestations were cerebral. Prior to 1928 it was generally assumed that the syndrome was due to renal insufficiency and "acute uremia." Oppenheimer and Fishberg disputed this concept when they discovered from the investigations of Volhard [16] that the cerebral symptoms occurred most frequently without impairment of renal function. They ascribed the cerebral symptomatology to sudden elevations in arterial pressure superimposed on an existing hypertension. These resulted in cerebral vasoconstriction, edema of the brain and consequently elevated intracranial pressure.

4. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Ann. Int. Med. **41**:264-278 (Feb.) 1928.

5. Keith, N. M.; Wagener, H. B., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Ann. Int. Med. **41**:141-188 (Feb.) 1928.

6. Barship, M. M.: Hypertensive Encephalopathy with Complications, M. Bull. Vet. Admin. **18**:88-91 (July) 1941.

7. Davison, G., and Brill, N.: Essential Hypertension and Chronic Hypertensive Encephalopathy: A Clinico-Pathologic Study, Ann. Int. Med. **12**:1766-1781 (May) 1939.

8. McAlpine, D.: Hypertensive Cerebral Attack, Brit. M. J. **2**:990-993 (Nov.) 1935.

9. Campbell, A. M. G., and Davies, D. A.: Two Cases with Cerebral Crises, Guy's Hosp. Rep. **85**:191-194 (April) 1945.

10. Izquierdo, S. S.: Chronic Hypertension of Nervous Origin, J. Lab. & Clin. Med. **21**:235-243 (Dec.) 1935.

11. Fortune, C. H.: Hypertensive Disease of the Brain, Kentucky M. J. **35**:30-34 (Jan.) 1937.

12. Scheinker, I. M.: Hypertensive Disease of the Brain, Arch. Path. **36**:289-296 (Sept.) 1943.

13. Chase, W. H.: Hypertensive Apoplexy and Its Causation, Arch. Neurol. & Psychiat. **38**:1176-1189 (Dec.) 1937.

14. Thiebault, F.: Anatomico-Clinical Study of Cerebral Form of Arterial Hypertension, Renal, Cardiac, and Cerebral Lesions, Ann. de méd. **45**:184-215 (March) 1939.

15. Scheinker, I. M.: Hypertensive Encephalopathy, Monatsschr. f. Psychiat. u. Neurol. **102**:159, 1940.

16. Volhard, in Mohr, L., and Staehelin, R.: Handbuch der innern Medizin, Julius Springer, Berlin, 1918, vol. 3, p. 1342; cited by Fishberg.[25]

There are some, however, who object to the use of the term hypertensive encephalopathy as a nosologic entity because it is generally regarded as a secondary cerebral manifestation of conditions such as lead poisoning, eclampsia gravidarum, diffuse glomerulonephritis and malignant nephrosclerosis, none of which is identical clinically with the syndrome which Oppenheimer and Fishberg [4] originally described as hypertensive encephalopathy.

It is in the light of these objections, which, unfortunately, usage seems to have justified, that the term "recurrent hypertensive cerebral thrombosis" is employed in this paper.

Clinically, the disease is one which usually affects young or middle-aged persons of either sex. It may appear with dramatic suddeness, or it may be initiated by a series of minor episodes attended by prodromal symptoms of headache, vertigo, vomiting, indigestion, weakness and paresthesias.

The onset may be marked by the appearance of mild mental symptoms. Neurologic signs are frequently absent at first, although they may be the initial symptoms. These symptoms may, and as a rule do, occur long before any clinical or laboratory evidence of renal or cardiac impairment appears. Early in the disease there are often transient periods of irritability, confusion, restlessness and sometimes assaultiveness. Many of the neurologic symptoms are fleeting, although there may be residual defects. Impairment of memory and emotional instability usually indicate irreversible damage to the brain structure. The severer attacks are characterized by epileptiform convulsions, attacks of blindness, temporary hemiplegia or monoplegia, dysesthesia, dysarthria and coma.

Impairment of the intellect may occur in the early stages of the disease, but, in general, frank psychosis does not become permanently fixed until the later phases of the disease, when there is extensive involvement of the cerebral arterioles and capillaries and widespread degeneration of nerve cells. It must be kept in mind that in certain cases the hypertensive syndrome may precipitate psychotic symptoms at any stage of the illness. This is apt to occur in patients who have latent psychotic tendencies. However, in the present group of cases, psychosis did not become permanently fixed until late in the disease and could therefore be regarded as an omen of grave prognostic significance.

Hypertension is the *sine qua non* of the syndrome. One of the reasons, nevertheless, that the correct diagnosis may be overlooked is that very often the blood pressure readings are within normal limits at the time they are taken. As Alvarez [2] stated, "It is the patient and not the doctor, who oftentimes recognizes that something has gone wrong with his brain."

Many of these patients have extremely labile blood pressures which tend to respond violently to emotional stimuli. During these moments of hypertensive stress, the patient may become irritable, unreasonable, vulgar and even assaultive. He may even lose consciousness for a few minutes and emerge in a state of confusion which may persist for several days or a week. During the attack the blood pressure is elevated but it may quickly drop back to normal levels, and when the physician examines the patient he may find no evidence of hypertension. It is important, therefore, in these cases not to rely on single blood pressure readings but to test the patient for hypertensive lability.

Detailed and excellent pathologic and clinical pathologic reports of this syndrome have appeared recently in the literature. In all these studies, the most important pathologic changes have been found in the cerebral arterioles. Davison and Brill,[7] reporting 7 cases, found the outstanding vascular changes to consist of arteriosclerosis with intimal proliferation, narrowed lumens of precapillary arterioles, marked hypertrophy of the media with increased numbers of nuclei and hyaline degeneration of the media. Parenchymatous degenerations were secondary to the vascular changes. These authors found that the brain was more extensively involved than other organs.

Paterson [17] related the cerebral thromboses, angiospastic attacks and cerebral hemorrhages in 2 cases to the presence of intimal capillary hemorrhages which he attributed to an increase of capillary pressure associated with loss of support due to atheromatous degeneration about the capillary. This point of view is shared by others (Winternitz and co-workers [18]). Scheinker [19] found that the most constant and uniform alteration consisted in a specific process characterized by hyaline degeneration and fibrous thickening of the arterioles and capillaries. He differentiated the arteriolar alterations associated with hypertension from simple arteriosclerosis by the term "hypertensive hyaline arteriolopathy."

More recently, Scheinker [20] attributed the cerebral hemorrhages in hypertensive disease of the brain to structural changes in the walls of

17. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage in the Causation of Cerebral Vascular Lesions, Arch. Path. **29**:345-354 (March) 1940.

18. Winternitz, M. C.; Katzenstein, R.; Mylon, E.; Murphy, J. P., and Zimmerman, H. M.: The Brain in Experimental Vascular Disease, Yale J. Biol. & Med. **13**:579-594 (May) 1941.

19. Scheinker, I. M.: Cerebral Thromboangiitis Obliterans (Histogenesis of Early Lesions), Arch. Neurol. & Psychiat. **52**:27-33 (July) 1944. Footnotes 12 and 15.

20. Scheinker, I. M.: Changes in Cerebral Veins in Hypertensive Brain Disease: Clinical Pathologic Study, Arch. Neurol. & Psychiat. **54**:395-408 (Nov.-Dec.) 1945.

the venules, consisting in extreme atrophy, advanced degenerative changes and even necrosis.

The object of this report is to submit additional pathologic evidence that the syndrome is, indeed, a nosologic entity which merits the "need of close correlation of the clinical phenomena with the result of morphologic studies of the cerebral lesions." [3]

Since the neurologic or mental symptoms antedated renal or cardiovascular disease in these cases, a comparison of the vascular lesions in the brain, kidneys, heart and aorta was carried out. In the majority of cases there was no difficulty in evaluating comparative degrees of sclerosis in the vessels of the brain, kidneys and heart merely by careful observation of the relative thickness of the vascular walls and reduction in the calibers of the lumens. Associated parenchymal lesions served as an additional guide in evaluating the relative degrees of vascular disease.

REPORT OF CASES

CASE 1.—J. D., aged 65 years, at the age of 45 years was obliged to stop working because of severe headaches, fits of shaking (epileptiform seizures?), frequent periods of restlessness, irritability, dizziness and overtalkativeness, associated with high blood pressure. When he felt well, he was kind, good natured and easy to get along with. Several times a week, however, he would experience transient episodes of irritability and talkativeness apparently related to the hypertension.

One year prior to admission, at the age of 64 years, he had a shock, after which he became confused, hallucinated and irrelevant. He lost weight and showed deterioration of memory. When he was admitted to the hospital his blood pressure was found to be 145 systolic and 60 diastolic. He exhibited some evidence of parkinsonism. Laboratory studies revealed a normal spinal fluid and negative serologic reactions of the blood. The blood contained 82 mg. of nonprotein nitrogen and 140 mg. of sugar per hundred cubic centimeters. Albuminuria and granular casts in the urine were reported.

When he was transferred to the State Hospital for Mental Diseases, shortly before his death, his blood pressure was 200 systolic and 100 diastolic. He was confused and disoriented and remained so until his death, one and one-half months after admission and twenty years after the onset of symptoms.

Death was due to acute glomerulonephritis and hypostatic pneumonia. Despite the prolonged history of hypertension, the patient's heart weighed only 400 Gm. There was but a moderate degree of sclerosis of the coronary arteries. The kidneys, though swollen, showed evidence of arteriolarsclerotic atrophy.

The brain weighed 1,220 Gm. There was some convolutional atrophy of the temporal and occipitoparietal areas. The large vessels at the base of the brain were mottled with moderate numbers of fatty and hyaline plaques, but the vascular lumens were not seriously embarrassed by these lesions. When the brain was sectioned, a number of discrete glossy nodules which ranged between 1 and 2 mm. in diameter were observed in the cortexes of the parietal and left occipital lobes. Two small ancient encephalomalacic cysts were encountered in the putamens. A few recent petechial hemorrhages were found in the vicinity of the right cerebellar dentate nucleus.

Sections of brain from the frontal, temporal, parietal and occipital lobes and from the motor projection area, midbrain, cerebellum and pons were stained with toluidine blue (Nissl), sudan III and King's silver carbonate (modification of Bielschowsky's stain).

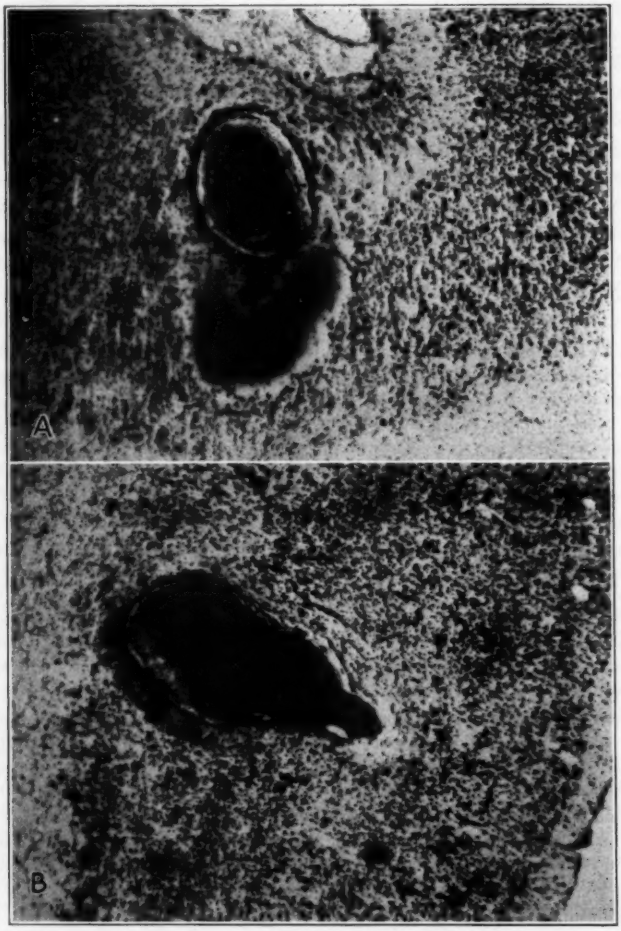

Fig. 1 (case 1).—*A*, revascularized arteriolar thrombus in cerebral cortex with perivascular effusion of fluid into the lower lamina. *B*, distended and thrombosed cortical capillary or venule, showing marked degeneration (hyalinization) of its wall. Toluidine blue; × 40.

The most striking type of vascular lesion was far advanced hyaline sclerosis of the arterioles, capillaries and some of the medium-sized vessels of the brain and pia mater. One of the cortical arterioles was tremendously dilated by an

organized and recanalized thrombus through which a fresh hemorrhage had escaped into the subjacent parenchyma (fig. 1 *A*). Corresponding to the discrete glossy lesions visible grossly in the cortex was another greatly distended vessel whose lumen was filled with a thrombus composed of conglutinated red blood cells (fig. 1*B*). The walls of these vessels were degenerated. Many of the arterioles and even medium-sized arteries exhibited lipid degeneration of their medial and intimal layers.

An occasional arteriole showed subintimal hemorrhage. Associated with these vascular lesions were many foci of necrobiosis in both the white and the gray matter. Areas of cellular devastation and diffuse glial proliferation were commonly encountered. In some areas the cellularity of the cortex was maintained by virtue of increased numbers of astrocytes, despite loss of nerve cells. A few small argentophilic plaques were scattered throughout the cortex. There were no Alzheimer cell changes, however, and the number of plaques did not exceed that found in the brains of normal elderly persons.

In the kidneys an acute glomerulonephritis and advanced renal arteriolarsclerosis were disclosed. The glomeruli were swollen and infiltrated with leukocytes, and in some instances there were hemorrhagic exudates in Bowman's spaces.

The heart presented a picture microscopically of interstitial edema and moderate sclerosis of the branches of the coronary arteries. It is noteworthy that the severity of vascular disease in the heart and kidneys did not equal that present in the brain.

The adrenal glands had undergone partial liquefaction but were otherwise not remarkable. No significant changes were observed grossly in the thyroid gland.

Comment.—The duration of this patient's illness was about twenty years, longer than is usually stated in the literature. In one report [7] the average span of life following the onset of symptoms was five years. The longest was thirteen years.

The lesions in the putamen must have occurred early because of the history of tremors for many years. As time passed, a succession of relatively small arteriolar thromboses undoubtedly occurred, which finally led to the development of a frank psychosis, one year before death.

Pathologically, arteriolar disease was the outstanding feature. This consisted of hyaline and fatty degeneration of the media and intima, intramural arteriolar hemorrhages, arteriolar thromboses, occasionally with recanalization of the thrombus, and capillary fibrosis.

Parenchymal changes were more diffuse than were the vascular lesions. They consisted in diffuse and focal loss of nerve cells, astrocytic overgrowth and lipid degeneration of the nerve cells. Some of these changes could be ascribed to the arteriolar disease. The more diffuse lesions were perhaps related to the customary process of aging.

CASE 2.—J. A., aged 54 years, at the age of 23 had a stroke. A second stroke occurred three years later, at the age of 26, and the third stroke at the age of 53 years. The last shock produced unconsciousness for several minutes and a hemiplegia of the right side which cleared up fairly rapidly. The patient became confused and irrational. Signs of cerebral deterioration, however, had begun to

set in four years previously; they consisted in lapses of memory, inability to maintain conversation and stuttering.

When the patient was brought into the hospital after the third stroke, his blood pressure was found to be 180 systolic and 100 diastolic. Lumbar puncture disclosed normal dynamics of the spinal fluid, a trace of globulin, moderate elevation of the colloidal gold curve and a total protein content of 95 mg. per hundred cubic centimeters. Serologic reactions of the blood and Wassermann reactions of the spinal fluid were negative. Roentgenograms of the chest and skull revealed normal conditions.

The patient's physical condition improved rapidly, but because of his mental state he was transferred to the State Hospital for Mental Diseases. He was cheerful, talkative and confused, showing pronounced flightiness and emotional lability. On one occasion his blood pressure was 190 systolic and 100 diastolic, and on another it was 220 systolic and 100 diastolic.

Laboratory studies revealed a moderate secondary anemia. Values for blood urea nitrogen and blood sugar were within normal limits. Repeated analyses of the urine revealed a heavy trace of albumin in only one specimen. Examination of the spinal fluid showed a normal colloidal gold curve, but the total protein was elevated to 116 mg. per hundred cubic centimeters and the Pandy reaction was positive. The cell count was within normal limits.

Three months after admission, the patient had a series of convulsions, starting in his right leg and eventually spreading over the entire body. Shortly thereafter he suddenly became agitated, destructive and uncooperative, refusing to take anything except fluid nourishment. This behavior continued for about two weeks and was followed by stupor and finally death, thirty-one years after the initial symptoms and six months after admission to the hospital.

At necropsy, the patient was found to be moderately emaciated. There was a confluent bronchopneumonia in the right lung. The heart weighed only 375 Gm., and the left ventricle was moderately hypertrophied. The coronary arteries were moderately sclerotic.

The kidneys weighed 255 Gm. The thyroid gland was slightly enlarged, weighing 25 Gm. It was diffusely rich in colloid.

As in the previous case, the essential pathologic change was found in the brain. It weighed 1,325 Gm. and was swollen and edematous. The pia-arachnoid membranes were thin and transparent. The basilar-cerebral arteries were beaded with rather flat yellowish fatty plaques which did not seriously impair the vascular lumens.

When the brain was sectioned, lesions similar to those described in the previous case were encountered. They consisted of small round circumscribed, dark purple glossy nodules, confined almost exclusively to the cortexes of both cerebral hemispheres. They varied in diameter from the size of a pinhead up to 2 mm. Sometimes they extended through the entire width of the cortical ribbon. They were more numerous on the right than on the left. One of these lesions was found in the cortex of the right cerebellar hemisphere. There was an old encephalomalacic cyst in the white substance of the rostral portion of the left occipital lobe. It was walled off by a firm brownish membrane. There was another scar in the left cerebellar hemisphere. A more recent area of softening was encountered in the confluent white matter of the frontal and temporal lobes.

Blocks were taken for histologic studies from representative areas of the brain. The frontal and temporal lobes and basal ganglia were stained by the Lepehne-Pickworth method for demonstrating cerebral blood vessels. Alternating sections were stained with sudan III and von Braunmühl's silver stain.

Sections from the left prefrontal area, left motor projection area, left cornu ammonis, left occipital lobe, right and left cerebellar hemispheres, basal ganglia, mammillary hypothalamus, midbrain and medulla oblongata were stained with toluidine blue (Nissl).

In the Lepehne-Pickworth preparations, the areas of thrombosis could be clearly seen. They were much more numerous than was apparent in the gross specimen since many of them were microscopic (fig. 2 *A* and *B*). The thrombosed vessels were enormously ballooned out into spherical (fig. 3*A*) or fusiform structures (fig. 3*B*). These aneurysmal-like dilatations were often surrounded by zones of

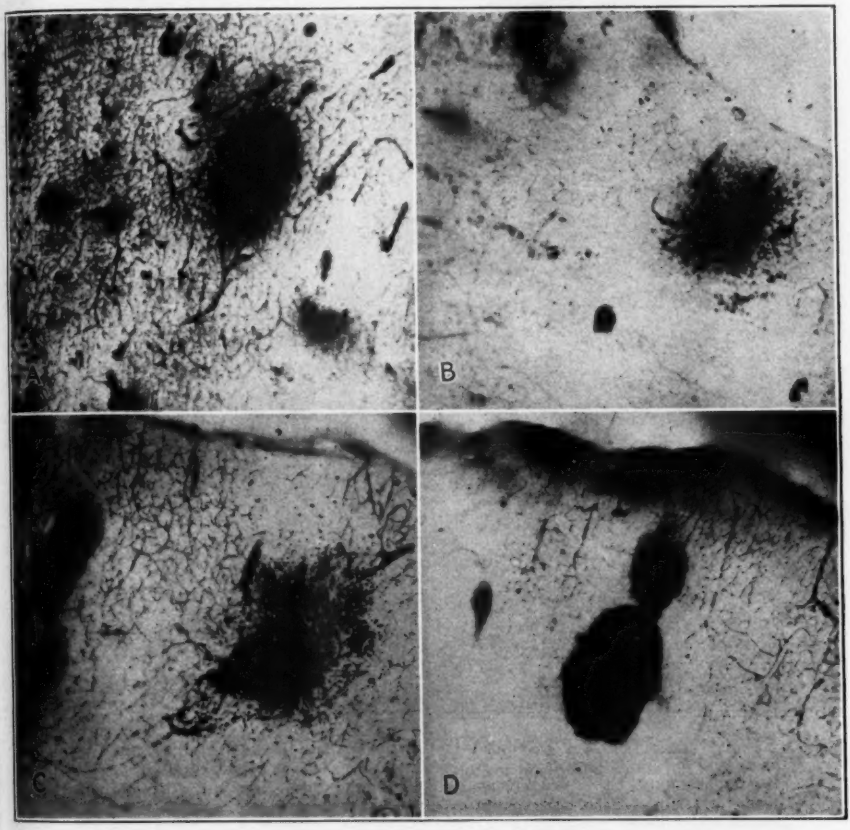

Fig. 2 (case 2).—Benzidine (Lepehne-Pickworth) preparations of the cerebral cortex showing aneurysmal-like dilatations of the arterioles, with perivascular effusions of blood (*A*, *B* and *C*). Note the many tiny capillary thromboses in the surrounding areas (*A*, *B* and *D*). Also note the segmented appearance of thrombosed vessels in *C* and *D*. + 26.

extravasated erythrocytes or plasma. In places where it was possible to trace the course of the thrombosed vessel through the cortex, a constant finding of

considerable significance was the constriction of the arteriole proximal and distal to the ballooned out segment (figs. 2 *C* and 3 *A* and *B*). Occasionally a "dumb-bell"-shaped thrombosis was encountered resulting from a short constricted segment intervening between two thrombosed areas in the same vessel (fig. 2 *D*).

The perivascular extravasations of blood appeared to be due to diapedesis rather than rupture of the arteriolar walls. In these thick sections (300 to 350 microns) it was often possible by adjusting the focus up and down to discern the expanded outline of the thrombosed segment. In no case could a break in the wall be found.

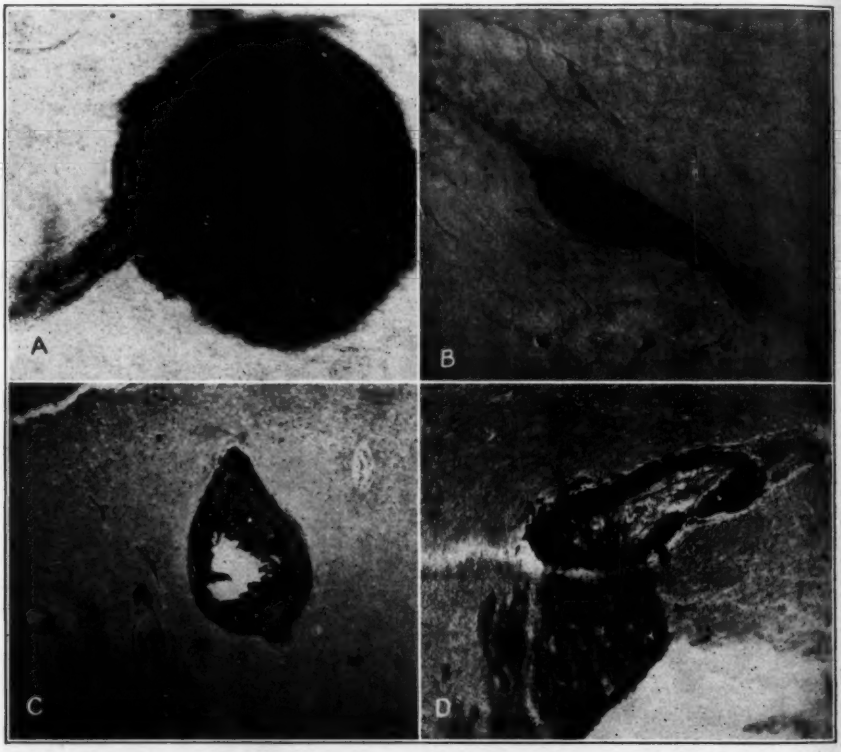

Fig. 3 (case 2).—*A*, ballooned-out cortical arteriole showing relative constriction of proximal and distal portions of vessel. Benzidine (Lepehne-Pickworth) stain; × about 72. *B*, fusiform aneurysmal-like distention and thrombosis of cortical arteriole. Note how dilatation extends for a short distance into proximal portion while distal portion is constricted and devoid of blood. Lepehne-Pickworth; × 25. *C*, thrombosed vessel in cortex showing extensive fatty degeneration of the entire circumference of its wall. Sudan III; × 25. *D*, almost complete fatty replacement of the media of one of the dilated but not thrombosed cortical arterioles. Sudan III; × about 72.

The sudan III preparations revealed significant changes in the affected arterioles. Of particular interest was the extensive fatty degeneration of the medial coat as well as of the intima of the ballooned-out thrombosed segment of the arterioles

(fig. 3 *C*). Some arterioles, not thrombosed but slightly dilated, showed almost solid rings of neutral fat in their walls (fig. 3 *D*). The intima was often most severely involved. In some instances the lumen of the arteriole was obscured, if not obliterated by the encroachment of a large subintimal fatty plaque (fig. 4 *A*). The majority of venules harbored scavenger cells laden with neutral fat globules in their perivascular spaces.

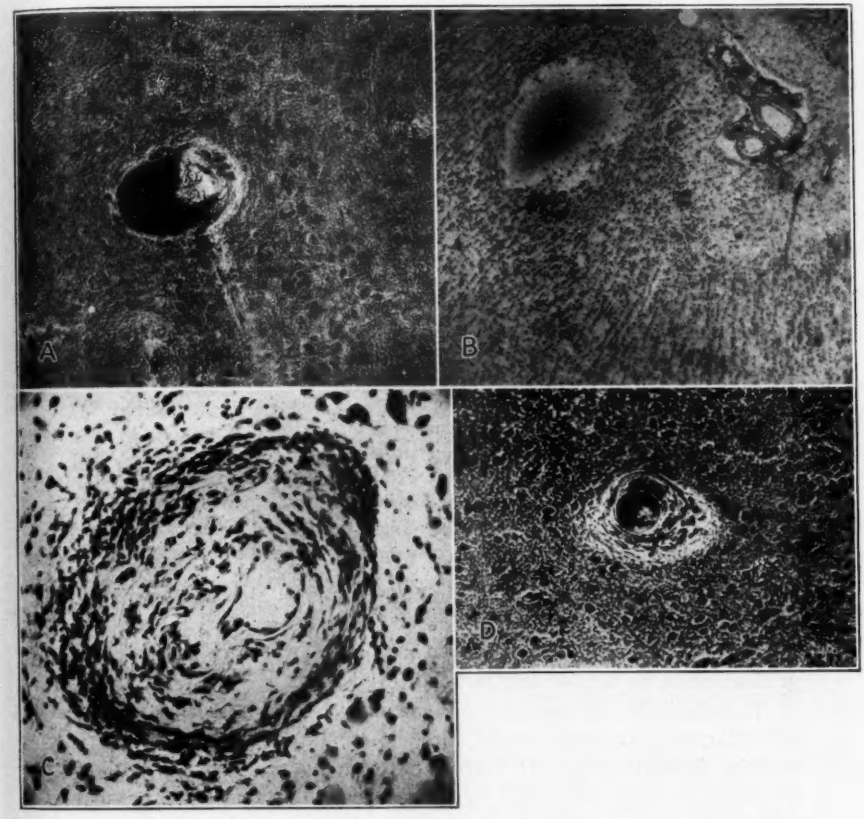

Fig. 4 (case 2).—*A*, compression of the lumen of an arteriole by a huge crescent-shaped subintimal fatty plaque. Sudan III; × 58. *B*, formation of a small cavity in the cortex by an effusion of plasma with relatively little destruction of nerve cells. Note the sclerotic and hyalinized arterioles in the adjoining areas. Toluidine blue; × 25. *C*, subintimal and adventitial fibrosis with medial hypertrophy of an arteriole in the cerebral cortex. The caliber of the lumen is greatly diminished. Note the perivascular infiltration of small round cells and the presence of swollen astrocytes in the perivascular stroma. Toluidine blue; × about 145. *D*, an arteriole in the cortex exhibiting concentric cellular hyperplasia of the media and considerable deposits of neutral lipids in the intima and media with almost complete obliteration of the lumen. Also note the large amounts of sudanophilous material (black) within the majority of nerve cells. Sudan III; × about 40.

Undoubtedly, some of the expanded thrombosed vessels in the cortex were venules or capillaries. In either case the thin vascular wall contained ample deposits of sudanophilous material.

The sudan III stain also disclosed extensive fatty degeneration of the nerve cells. Lipid-bearing scavenger cells were present in the interstitial stroma.

The von Braunmühl preparations revealed a small number of argentophilic plaques showing a predilection for the tissues adjoining sclerotic arterioles.

In the toluidine blue (Nissl) preparations, the diffuse nature of the cerebral arteriolar sclerosis was clearly evident. The cerebral cortex was disrupted by areas of devastation, glial scars and areas of partial softening occupied by compound granular corpuscles. In one area of the cortex there was an oval-shaped plasma-filled space compressing the nerve tissue (fig. 4 *B*). The cortex was invaded by many swollen fibrous astrocytes (*gemästete Zellen*), and there were numerous perivascular foci of gliosis, both in the gray and in the white substance. In the cerebellum an entire folium had undergone ischemic necrosis due to infarction.

The pial as well as the intrinsic cerebral arterioles and capillaries were extremely sclerotic. Some vessels displayed homogeneous hyaline thickenings with complete loss of cellularity. Others showed concentric cellular hyperplasia of the media and adventitial and subintimal fibrous proliferation with considerable reduction of the lumen. One such vessel, shown in figure 4 *C*, was also partly surrounded by small round cells and astrocytes. Occasionally an arteriole showing subintimal hemorrhage and thrombosis was encountered.

An arteriole whose lumen was practically obliterated by a crescent-shaped subintimal fatty plaque is shown in figure 4 *D*. There was also considerable concentric fibroplastic cellular hyperplasia of the media.

The kidneys showed pronounced interstitial fibrosis with scarring of many of the glomeruli. The renal arterioles exhibited advanced stages of hyaline sclerosis though not as extreme as that of the cerebral arterioles.

In the heart, there were small focal zones of myocardial scarring but the arterioles were much better preserved than in either the kidneys or the brain.

Comment.—The interesting clinical features in this case were the recurrent attacks of cerebral arteriolar thromboses over a period of thirty-one years, the tendency toward rapid recovery and the late but gradual onset of mental deterioration.

Pathologically the outstanding vascular changes consisted of (1) arteriolar, capillary and venular thromboses; (2) subintimal and perivascular hemorrhages; (3) marked fatty degeneration of the intima, the media or both, with focal weakening and dilatation of the vascular walls; (4) focal cortical aneurysmal-like dilatations of arteriolar and capillary walls and diapedesis; (5) hyaline degeneration of the arterioles and capillaries, and (6) subintimal and adventitial fibrosis with medial hypertrophy.

The essential lesions in the brain tissue consisted of localized areas of edema in the vicinity of the thromboses and diapedeses, old scars and more recent areas of softening and glial proliferation, perivascular gliosis, chronic disease of the nerve cells, marked fatty changes of the nerve cells and small numbers of argentophilic plaques.

Emphasis is placed on the fact that only the small vessels of the brain showed the severest changes, and most of these were the cortical arterioles.

The correlation that is suggested by the pathologic findings, especially those demonstrated in the Lepehne-Pickworth and sudan III preparations, is that hypertensive and cerebral vasospastic episodes were constantly recurring events. These attacks initiated a series of changes in the brain which, owing to frequent repetition, ultimately resulted in degenerative arteriolar and capillary changes as well as in secondary degeneration of brain tissue.

In the primary stages the vasospastic attacks resulted only in transient cerebral ischemia and edema. However, it is obvious that repeated functional contraction of the vessels, if sufficiently strong, may eventually lead to necrosis of brain tissue. The medial hypertrophy of the arterioles indicated that the normal effect of vasoconstriction had been aggravated and made permanent.[5]

Thromboses could have resulted in two ways. After the hypertensive overstretching of the arteriole, it underwent vasoconstriction. That portion of the vessel unable to contract because of fatty degeneration of its muscular layer remained distended with blood. Stasis, diapedesis and, eventually, coagulation took place. Thrombosis may also have occurred as a result of hemorrhages into the vascularized intimas. According to Paterson,[17] these hemorrhages, due to increase of intracapillary pressure associated with loss of perivascular support, cause local arterial spasms resulting in thrombosis.

It is readily apparent from the illustrations in this and in the previous case that the perivascular extravasations and edema might cause transient functional impairment of a much larger area than that supplied by the thrombosed arteriole. The tendency toward fairly rapid remission of symptoms, especially in the early stages of the disease, is probably related to the absorption of the fluid and blood and the restoration of the function of the majority of neurons.

CASE 3.—Ruth C, a 47 year old white woman, started to complain of severe headaches and blurred vision at the age of 41 years. She became depressed and entertained paranoid ideas. After three years she was finally committed to a mental hospital from which, after resting for six weeks, she was discharged in an improved condition. It was found that she had been suffering from a marked degree of hypertension. Her blood pressure was 210 systolic and 120 diastolic. The blood Wassermann reaction was doubtful, but the Hinton reaction was negative. The spinal fluid Wassermann reaction was negative. There was a slight trace of albumin in the urine.

After five or six months she suffered a relapse and was again committed. She displayed marked emotional fluctuations. The hypertensive level previously noted was still present. In addition, examination of the eyegrounds revealed a hypertensive retinosis with retinal exudates and old retinal hemorrhages. Other

significant physical findings were a residual right hemiplegia, palsy of the right side of the face, absence of gag reflex and paresis of the right pterygoid muscles. Her blood pressure on admission was 280 systolic and 150 diastolic. The serologic reactions of the blood were negative. Hyaline casts and a moderate amount of albumin were present in the urine. The blood urea nitrogen level was 16.3 mg. per hundred cubic centimeters.

Six and one-half months after admission she suddenly collapsed. She died two days later, about five and one-half years after the onset of symptoms.

The cause of death was a massive cerebral hemorrhage into the region of the left basal ganglia with rupture into the lateral ventricle. There were many glossy circumscribed nodules in the cortex, similar to those described in the previous cases. Many smaller hemorrhages were scattered throughout the brain substance.

The basilar artery showed a marked degree of sclerosis. The arteries of the circle of Willis were moderately sclerotic.

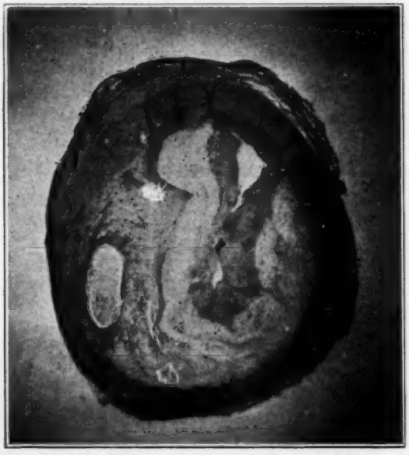

Fig. 5 (case 3).—Obliterating atherosclerosis of the left common carotid artery at the aortic ostium. Hematoxylin and eosin; × 5.

The heart weighed 480 Gm. The wall of the left ventricle was hypertrophied, measuring 25 mm. in width. There was a moderate degree of coronary sclerosis.

The orifice of the left common carotid artery was practically obliterated by a huge atherosclerotic plaque (fig. 5). The aorta displayed only a moderate degree of atherosclerosis.

In the liver there was a circumscribed node 1 cm. in diameter which proved to be a benign hepatoma. There was a small benign papillary adenoma in the isthmus of the thyroid gland.

Histologic studies of the brain revealed endarteritis obliterans and widespread arteriolosclerosis with extensive fatty degeneration of the vascular walls (fig. 6). One arteriole showed a heavy eccentric perivascular exudate of small round mononuclear cells. Its lumen was reduced to a tiny slit by a row of swollen foamy cells in the thickened intima (fig. 7).

Foci of softening composed of compound granular corpuscles or areas of glial scarring were frequently in close proximity to the sclerotic arterioles. In addition to these alterations, there were intense capillary and venous engorgement and many perivenous hemorrhages.

No argentophilic plaques were seen in the silver preparations. The arteriosclerotic plaque in the left common carotid artery was composed of partly hyalinized connective tissue, split up by masses of cholesterol-like deposits and small necrotic patches with cellular debris. In the deep portion of the media, there was a recent hemorrhage. The vasa vasorum were sclerotic.

The microscopic sections of the kidneys showed far advanced hyaline sclerosis of the arterioles and medium-sized arteries, fibrosis of the glomeruli and marked

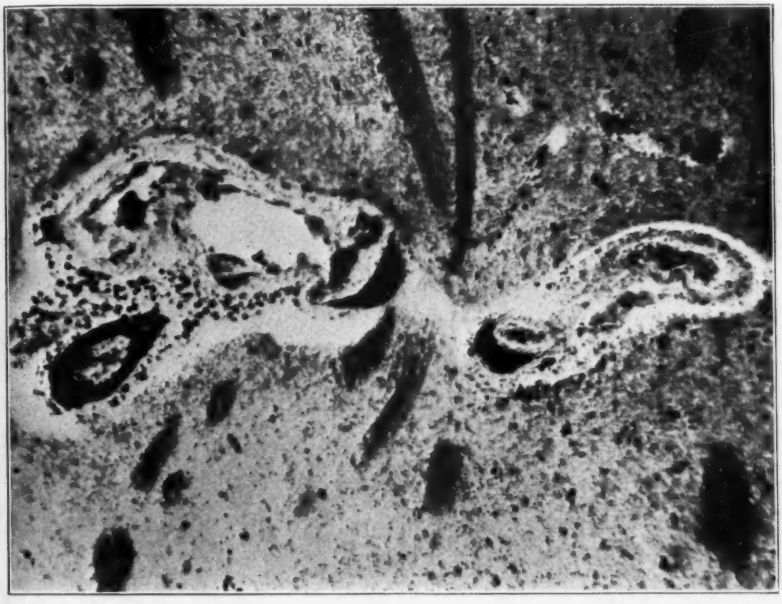

Fig. 6 (case 3).—Extensive and incomplete fatty changes of vessel walls. Note the large numbers of histiocytes laden with neutral fat in vicinity of vessel showing solid ring of fat. Sudan III; × 100.

interstitial fibrosis (fig. 8). There was no evidence of specific changes in the wall of the aorta.

Comment.—In this case it appeared as though nature had carried out a modified Goldblatt operation by gradually constricting the lumen of the left common carotid artery by a slowly progressive obliterating atherosclerosis. It may have been coincidental that the massive cerebral hemorrhage occurred on the same side as the sclerotic carotid artery. It is noteworthy, however, that arteriolosclerotic disease of the brain was just as severe on the right side as it was on the left. Comparison

of cardiac, renal and cerebral arterioles showed less severe involvement of the heart than of the other two organs.

CASE 4.—Francis T., a 47 year old white man, suffered his first shock at the age of 37 years. He lost consciousness for several days. At that time he was reported to have had hypertension. Six years later two more similar attacks occurred six months apart. He complained of extremely severe fronto-occipital headaches which usually lasted for twenty-four hours. Then he noticed that his vision was failing. This was climaxed six weeks before his admission by a sudden attack of transitory blindness without loss of consciousness.

Two years before his death, he suddenly experienced a severe headache with nausea and vomiting. He was dull and drowsy. His blood pressure was 200 systolic

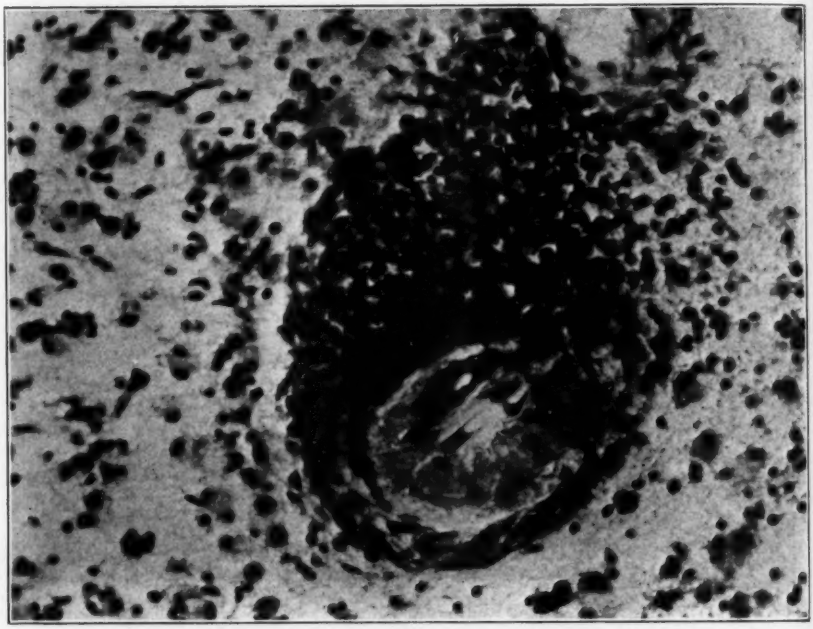

Fig. 7 (case 3).—Endarteritis obliterans of a vessel in the putamen. The dense perivascular round cell infiltration is possibly related to the close proximity of the vessel to a focus of softening not shown in this picture. Note the medial hyperplasia and the compression of the lumen by swollen, vacuolated foam cells. Enormous numbers of swollen astrocytes are seen in the perivascular region. Toluidine blue; × 250.

and 120 diastolic. He had a complete left homonymous hemianopsia and blurred disk margins. His spinal fluid was xanthochromic and under increased pressure. Mosenthal tests disclosed impairment of renal function.

The past medical history revealed that at the age of 26 years the patient had been treated for gonorrhea and syphilis. Later, because of a persistent positive serologic reaction, he received continuous antisyphilitic therapy for four years, after which his blood and spinal fluid remained negative serologically.

When he was admitted to the State Hospital for Mental Diseases he was profoundly deteriorated and almost blind. His blood pressure had fallen to 195 systolic and 100 diastolic. Hearing was impaired. There were a left homonymous hemianopsia and bilateral papilledema. Examination of the spinal fluid showed normal dynamics; the total protein was 24 mg. per hundred cubic centimeters, and the Wassermann reaction was negative. Serologic reactions of the blood were negative, and blood chemistry values were within normal limits.

The patient's course in the hospital was quite remarkable. He was not expected to live, yet from day to day he showed rapid improvement. Although his blood pressure remained at the high level of 200 systolic and 100 diastolic, his mental confusion rapidly cleared. His eyesight improved, and by the end of

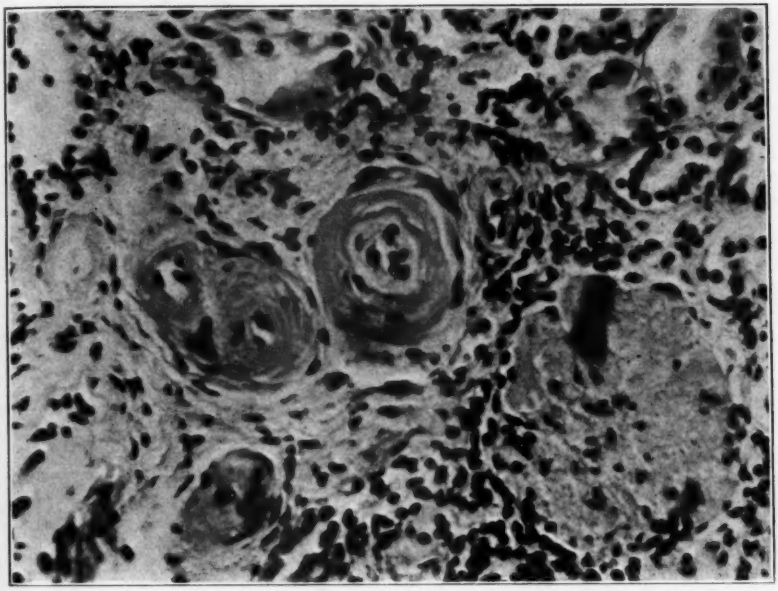

Fig. 8 (case 3).—Renal arteriolarsclerosis, interstitial fibrosis and hyalinization of glomeruli. Hematoxylin and eosin; × 250.

two weeks after admission the papilledema had completely subsided and the fundi resumed a normal appearance. Psychotic symptoms receded completely, leaving a person of fair intelligence, clean, neat and cooperative. Except for some emotional instability, patchy memory defects and a constant hypertension, the patient practically recovered. He was about to be discharged, when he was found in a semicomatose state with a right hemiplegia. His blood pressure was 225 systolic and 135 diastolic. He died nine hours later, ten years after the onset.

The cause of death revealed by necropsy was a massive hemorrhage in the left cerebral hemisphere which had destroyed the left basal ganglions and had ruptured into the left lateral ventricle. There was a large old encephalomalacic cavity lined by a thin brownish-stained membrane in the right temporal lobe.

Small hemorrhages were scattered throughout the midbrain and pons. Older areas of softening and cavitation appeared in both temporal lobes, and colorful scars in the white substance of the temporal, parietal and occipital lobes were also encountered.

The histologic changes were of interest because they were similar to those in the preceding cases. There was a pronounced medial hypertrophy of the cerebral arterioles, frequently associated with intimal and adventitial fibrosis or hyalinization. In contrast to the advanced stages of arteriolar sclerosis, the larger caliber vascular channels, including the basilar and pial arteries, were relatively unaffected by the sclerotic process.

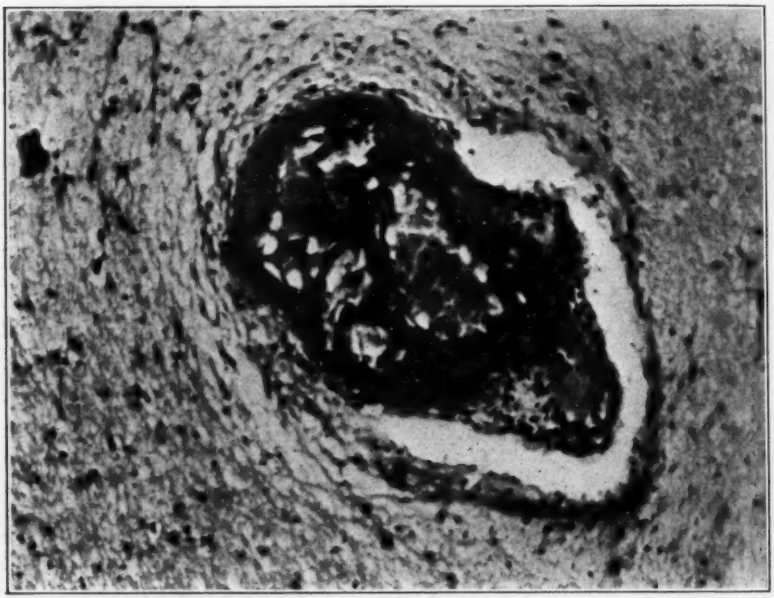

Fig. 9 (case 4).—Hyalinization and necrosis of wall of thalamic arteriole. Toluidine blue; × 150.

Extensive areas of softening and tissue rarefaction were associated with the diffuse arteriolar disease. In the right thalamus, where many perivascular hemorrhages had occurred, there was a vessel, part of whose wall appeared to have undergone hyaline necrosis (fig. 9). In another portion the intima was stripped away from the media by a subintimal hemorrhage. The arterioles of the optic nerves were markedly hyalinized and their lumens reduced to narrow slits. The Masson trichrome preparations disclosed the arteriolar thickening in many instances to be due partly to hypertrophy of the muscular media and partly to fibrous hyperplasia of the intima and adventitia. The renal arterioles were, by comparison with the cerebral vessels, but mildly sclerotic. Only a few small vessels showed marked hyaline thickening. The renal parenchyma was correspondingly well preserved. The heart weighed 460 Gm. The left ventricle was hyper-

trophied to a thickness of 23 mm. The coronary arteries were practically free of arteriosclerotic disease. The aorta showed a moderate degree of fibrous thickening of the intima and media, but no evidence of a specific lesion was present. The vasa vasorum were free of perivascular exudate.

Comment.—The interesting feature in this case is that, despite the long history of severe hypertension (ten years), the renal arterioles were relatively well preserved, whereas the cerebral arterioles showed the severest sclerotic changes.

CASE 5.—Eugene R., a 54 year old white man, for many years had had attacks of irritability and increasing memory failure. The outstanding symptoms occurred at the age of 48 years, when he had spells of dizziness and vomiting associated with falls. During one such episode, he was struck by a car while he was crossing the street. One year later he began to experience convulsive seizures which lasted only a few minutes. He became assaultive and profane toward his wife. He began talking to himself. One night he suddenly left his house and on his return was unable to talk.

He was sent to the hospital when examination disclosed a blood pressure of 190 systolic and 110 diastolic. He was confused and aphasic. Weakness of the right side and marked memory defects were noted. Because of failure to improve he was sent to the State Hospital. On admission his blood pressure was 222 systolic and 130 diastolic. The right-sided weakness had disappeared and results of the neurologic examination were essentially negative.

Laboratory studies revealed negative serologic reactions of blood and spinal fluid. The blood urea nitrogen level was 30.6 mg. and the creatinine level 1.6 mg. per hundred cubic centimeters. On several occasions slight to moderate traces of albumin appeared in the urine. The colloidal gold curve was 0000223100; the reaction for globulin was positive, and the total protein was 33 mg. per hundred cubic centimeters.

While in the hospital, the patient had numerous convulsions, some of which endured for as long as an hour. He was aphasic in both the expressive and the receptive spheres. His blood pressure remained high. After a series of convulsions he lapsed into a coma from which he recovered. Two months later, however, approximately six years after the appearance of symptoms, he died.

The essential observations at autopsy were the following: There was a confluent bronchopneumonia of the right lung and a strongly positive xanthoprotein reaction in the postmortem blood specimen, indicating terminal uremia.

The brain weighed 1,260 Gm. There were considerable subarachnoid edema and convolutional atrophy of the frontal lobes. The large vessels at the base of the brain showed only slight arteriosclerotic disease. Encephalomalacic cavities measuring up to 1.5 and 2 cm. in diameters were found in the right centrum ovale, both temporal lobes, the left putamen and thalamus and the right parietal and left occipital lobes. They were all lined with membranes stained with old blood pigment.

Histologic studies were carried out according to the following methods: toluidine blue (Nissl) was used for the left middle frontal gyrus, left motor area, left basal ganglia, left cornu ammonis, mamillary bodies and hypothalamus, midbrain and cerebellum; sudan III and von Braunmühl's method were used for the left frontal lobe, left insula and right cornu ammonis; Kultschitzky's method was used for the right frontal lobe.

The most striking features in the toluidine blue preparations consisted of marked hyalinization and thickening of the arteriolar and capillary walls, sometimes to the point of almost complete occlusion (fig. 10 *A*). The pial arteries and arterioles were not severely affected. Most of the cortical arterioles had

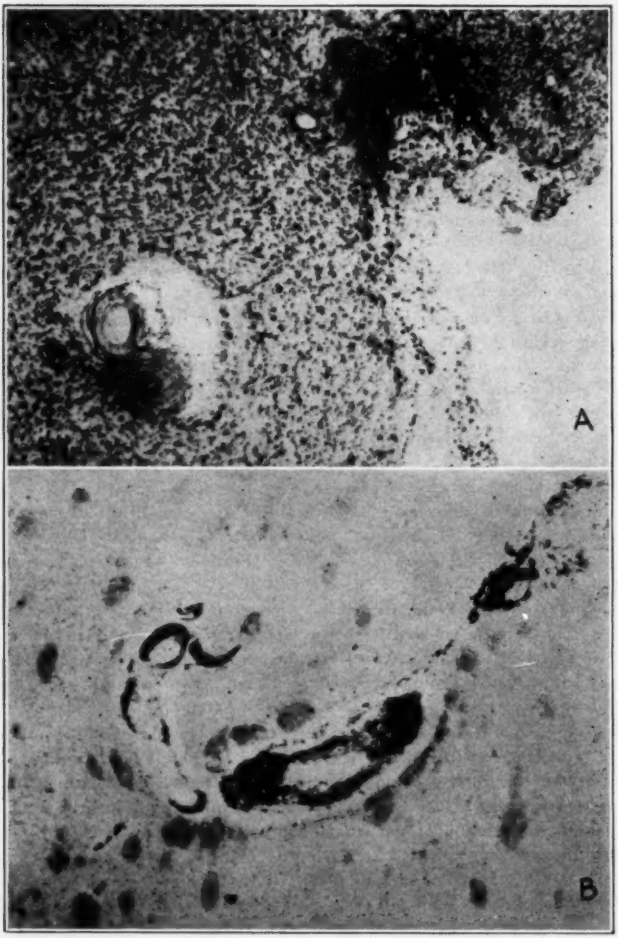

Fig. 10 (case 5).—*A*, almost total occlusion of hyalinized cerebral arteriole. Note the small focus of softening in the upper left corner. Toluidine blue; × 38. *B*, marked fatty changes in walls of dilated prearterioles, arterioles and capillaries. Sudan III; × 38.

hyalinized walls, but the cytoarchitecture of the cortex was not significantly altered.

In the sudan III preparations, some of the medium-sized arteries and arterioles showed far advanced fatty degeneration of their walls. In several, solid rings

of neutral fat encompassed the lumens. In the smaller vessels, streaks of lipid material were scattered through the wall. Scavenger cells laden with neutral fat globules were present in the perivascular spaces. Abnormal amounts of sudanophilous substance were also noted in the nerve cells. No Alzheimer plaques (argentophilic) or neurofibrillary disease was found in the silver preparations. The myelin preparation of the frontal lobe revealed some thinning out of the subcortical fibers and several ill defined areas of demyelination in the deeper portion of the white substance.

The renal arterioles were found to be as severely diseased as the cerebral vessels. This was accompanied with parenchymal atrophy and fibrosis. On the other hand, the myocardium, though hypertrophied, showed no gross or microscopic areas of scarring and the arterioles were fairly well preserved.

Case 6.—Salena M., a 49 year old white woman, about six months prior to her admission began to evidence a gradual change in personality. About two months before hospitalization she began to lose weight despite an unusually good appetite. She became untidy, indifferent to her personal appearance, confused and forgetful. She was brought to a physician who made the diagnosis of Bright's disease and hypertension. Her speech became thick and difficult to understand. Urinary incontinence developed, and she became destructive. She exhibited marked emotional lability.

Six years previously a Hinton test was found to elicit a positive reaction. The Wassermann reaction was negative. The clinical diagnosis of dementia paralytica and hypertension was therefore made.

On admission to the hospital her blood pressure was 180 systolic and 110 diastolic. She presented a picture of pronounced mental deterioration. There were some neurologic signs, such as sustained ankle clonus, instability of gait and variable Babinski responses.

The phenolsulfonphthalein sodium test indicated poor renal function although there was but slight albuminuria. Wassermann reactions of the blood and spinal fluid were negative. The blood sugar level was 83 mg. per hundred cubic centimeters, the nonprotein nitrogen level 37.5 mg. and the creatinine level 1.2 mg.

The patient's clinical course was steadily downhill, both physically and mentally, and she died approximately nine or ten months after the onset of her mental symptoms.

At necropsy, the appearance of the body was unusual. The face and trunk were emaciated, but the hips, thighs and legs were well nourished. There was a marked growth of hair over the upper lip. In the anterior lobe of the hypophysis, there was a small oval-shaped tumor whose histologic characteristics were completely obliterated by recent coagulative necrosis.

The brain weighed only 1,050 Gm. It was swollen and edematous. The left lateral and transverse dural sinuses were occluded by clotted blood. The middle ears showed no inflammatory changes. The large cerebral blood vessels were moderately sclerotic. Grossly, several types of lesions could be seen in the sectioned brain. A few small encephalomalacic cysts were present in the white matter of both frontal lobes. They averaged 2 to 3 mm. in diameter. There were several small and shallow defects in both putamens. A single glossy cortical nodule, similar to those described in the first 3 cases, was noted in the left middle frontal gyrus.

In the right half of the pons there was an irregular brownish linear area of scarring which extended through the recticular formation, and on the left side there was an encephalomalacic cyst 1.5 cm. in diameter.

Toluidine blue (Nissl) preparations of the left frontal lobe, motor area, hypothalamus, basal ganglia, temporal lobe, cerebellum, midbrain, pons, medulla and cervical portion of the spinal cord disclosed a severe and generalized sclerosis of the arterioles. For the most part the degenerative changes consisted in extreme

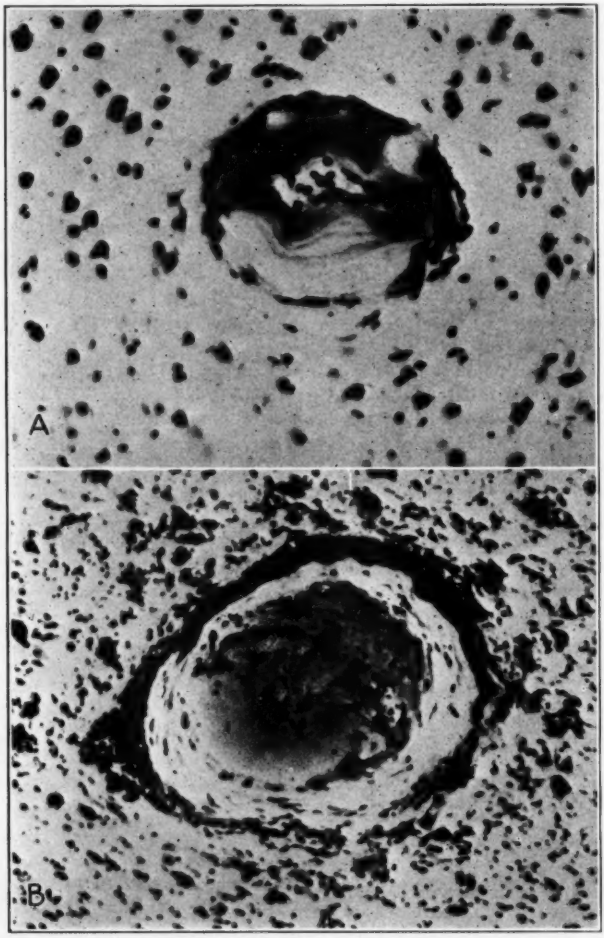

Fig. 11 (case 6).—*A*, marked hyaline degeneration in wall of thickened cortical arteriole. Toluidine blue; × 110. *B*, thrombotic occlusion of arteriole in caudate nucleus. Part of the wall has undergone hyalinoid necrosis. Note the slight perivascular infiltration of small round cells at the pole of the vessel. Toluidine blue; × 110.

stages of hyaline thickening of the medium-sized arteries, arterioles and capillaries (fig. 11 *A*). In the caudate nucleus, one of the vessels was occluded by a thrombus

and surrounded by a ring of astrocytes (fig. 11 *B*). The lumens of many of the arterioles in the insular cortex were practically obliterated by the thickened hyalinized vascular walls.

The parenchymal lesions consisted of focal areas of blanching, necrobiosis, partial softenings and perivascular gliosis. For the most part, however, the integrity of the cortical laminations was preserved. The nerve cells, however, were atrophied and chromatolytic.

The immediate cause of death was a suppurative interstitial nephritis and ascending pyelonephritis. The renal parenchyma was studded with tiny abscesses and areas of hemorrhagic infarction.

Independent of the acute inflammatory process, there was evidence in the form of partially fibrosed glomeruli, interstitial fibrosis and advanced arteriolar sclerosis that chronic renal vascular disease had preceded the acute infection. A comparison of the renal and cerebral arterioles showed an equal severity of sclerotic involvement.

The heart weighed 365 Gm. The coronary arteries and arterioles were but moderately sclerotic. This was associated with some increase of the interstitial and perivascular fibrous tissue in the myocardium.

The aorta was moderately atherosclerotic (2 +), but it showed no evidence of specific inflammatory lesions.

Comment.—This case presents several noteworthy features. The rapid downhill course was due to the suppurative renal infection. Clinically, the illness was ushered in by mental and neurologic symptoms resulting from recurrent cerebral arteriolar thromboses. It is possible, however, that a subacute glomerulonephritis may have been present at the beginning, although there was no evidence of this in the microscopic preparations of the kidneys. The history is not clear, since the patient was told she had Bright's disease some time after the onset of mental aberrations. She lived only nine or ten months after her illness began.

The rather sudden appearance of endocrinologic changes associated with an unidentified tumor of the anterior lobe of the hypophysis poses the question as to the role of this gland in the pathogenesis of the hypertension.

Despite the short duration of her symptoms, the vascular lesions in the brain and kidneys were as advanced as those seen in some of the patients with many more years of hypertensive symptoms.

COMMENT

An analysis of the clinical data shows that this disease affected persons through the second and fourth decades of life. The average age at onset was 40 years. The average age at death was 52.6 years. The youngest patient had his first attack at the age of 23 years and the oldest at the age of 48 years. The youngest patient to die was 47 years of age. The oldest to die was 65 years.

The average span of life was 11.4 years after the onset of hypertensive symptoms. This is twice as long as has been reported by others.[7]

One patient lived for thirty-one years despite repeated strokes and high levels of blood pressure. Another patient in whom an acute suppurative renal infection developed died ten months after her symptoms brought her into the mental hospital. This patient (case 6) also had an adenoma (type undetermined because of necrosis) of the anterior lobe of the hypophysis, and it is possible that this may have constituted an important endocrine factor in the pathogenesis of her hypertension.

The average systolic blood pressure was 223 mm. of mercury. The average diastolic pressure was 123 mm. of mercury. However, it must be noted that, for the most part, early blood pressure records were not available. Sometimes the patient was told that he or she had a high blood pressure, or else there was an inadequate history with reference to the existence of hypertension early in the disease.

Neurologic or mental symptoms or both were the initial manifestations in all our cases; therefore it was of interest to compare the vascular

TABLE 1.—*Comparative Degree of Arteriolar Disease in Various Organs*

Stage of Sclerosis	Brain, No. of Cases	Kidneys, No. of Cases	Heart, No. of Cases	Aorta, No. of Cases	Miscellaneous, No. of Cases
±	..	..	2	1	..
1+	..	..	..	2	..
2+	..	1	4	3	..
3+	..	3	..	..	..
4+	6	2	..	..	1 (optic nerve)

and parenchymal lesions in the brain, kidneys, heart and aorta. As mentioned earlier, this was carried out by careful observation of the relative thickness of the arteriolar walls, the reduction in the calibers of the vascular lumens and the degree of fatty degeneration of the vessel wall. Secondary parenchymal damage was utilized as an additional guide in evaluating the relative functional disease of the blood vessels. It is recognized that the validity of any conclusions based on such rough criteria would rightly be open to question, but for the purpose of this study it was deemed desirable but not essential to make quantitative measurements. Table 1 shows the results of these comparisons. In all 6 cases, vascular (primarily arteriolar) disease was maximal (4+) in the brain. In only 2 cases was the arteriolar disease in the renal parenchyma as diffuse and as severe as in the brain. In 3 cases arteriolar disease in the kidneys was far advanced (3+) but either less diffuse or associated with less microscopic parenchymal change than in the brain. In 1 case, there was hardly any comparison between the severe cerebral arteriolar sclerosis and the relatively mild involvement of the renal arterioles.

The arterioles of the heart were but moderately sclerotic in 4 cases and practically devoid of arteriosclerotic changes in 2 cases. The aorta showed the least changes.

One patient (case 4), who had transient attacks of blindness, showed severe (4+) arteriolar disease of the optic nerves.

Thus it is fairly clear that the disease is primarily one affecting the arteriolar system. The brain and kidneys were the most severely involved, especially the brain.

The coronary arteries and their terminal branches were spared to a surprising degree. None showed more than a moderate degree of hyaline thickening of their walls, and in no case were the vascular lumens embarrassed. In 2 cases, occasional focal myocardial scars were noted. The aorta showed mild to moderate stages of arteriosclerosis. Changes were confined chiefly to the intima. In 1 case there were a few microscopic scars in the media which were associated with advanced sclerosis of the vasa vasorum.

One of the most remarkable vascular lesions encountered in this series was an obliterating type of atherosclerosis of the proximal portion of the left common carotid artery, beginning at the aortic orifice (case 3, fig. 5). This case presents almost the human counterpart of the experimental hypertension produced in dogs by ligation of the various cerebral arteries (Nowak and Walker [21] and Fishback, Dutra and MacCamy [22]). The effect of alterations in cerebral blood flow on body blood pressure was demonstrated by Starling [23] in 1925, when he severed the brain of a dog from its own blood supply and supplied it from another circulatory system in which the rate of blood flow could be controlled. When the flow of blood to the brain was increased, the dog's body blood pressure dropped, and when the flow of blood to the brain was diminished the body blood pressure promptly rose.

One is led to wonder, therefore, whether the ischemic brain, like the ischemic kidney, may elaborate a humoral pressor substance which may set into motion the cycle of events leading to hypertension. This possibility has already been proposed by others,[22] but as yet no cerebral pressor substance has been reported.

RELATION OF CARDIAC HYPERTROPHY TO HYPERTENSION

Ordinarily in hypertensive cardiovascular disease, in which the renal factor plays a dominant role, cardiac hypertrophy is marked. In 48

21. Nowak, S. J., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension, New England J. Med. **220**:269-273 (Feb.) 1939.

22. Fishback, H. R.; Dutra, F. E., and MacCamy: The Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head, J. Lab. & Clin. Med. **28**:1187-1194 (July) 1943.

23. Starling, E. H.: The Physiological Factors in Hyperpiesia, Brit., M. J. **2**:1163, 1925.

cases of rapidly progressive hypertensive disease reported by Odel,[24] the average weight of the heart was 567 Gm. Only three hearts weighed less than 400 Gm. Keith, Wagener and Kernohan [5] found that the degree of cardiac hypertrophy in rapidly progressive hypertension was usually related to the duration of the hypertension.

In our series of cases, the average weight of the heart was 400 Gm. The largest weighed 480 Gm. Four hearts weighed 400 Gm. or less. No correlation could be established between the degree of cardiac hypertrophy, the highest levels of hypertension and the duration of illness (table 2). In 5 out of the 6 cases the left ventricular walls measured between 22 and 25 mm. in thickness. However, 1 patient (case 1), who had had hypertension for ten years, had a heart which weighed only 400 Gm. and whose left ventricular wall measured only 15 mm. in thickness.

TABLE 2.—*Cardiac Hypertrophy, Levels of Hypertension and Duration of Illness*

Case No.	Weight of Heart, Gm.	Thickness of Wall of Left Ventricle, Mm.	Highest Blood Pressure	Duration of Illness, Yr.
1	400	15	200/100	20
2	375	22	220/120	31
3	480	25	280/135	5½
4	460	23	225/135	10
5	320	23	222/132	6
6	365	25	190/100	10/12 (?)

It may be that the relatively mild degree of cardiac hypertrophy in the face of hypertension of many years' duration reflects the recurrent episodic nature of the hypertension in these cases. This would also explain the long duration of the illness, except in those cases terminated by massive cerebral hemorrhage or intercurrent infection.

This observation corresponds to the experience of Fishberg,[25] who stated that in cases of essential hypertension starting with cardiac insufficiency the nervous symptoms were apt to be minimal. In those cases, on the other hand, in which mental symptoms appeared first, the heart usually held out for a long time or to the end.

24. Odel, H. M.: Arteriolar Changes in the Myocardium in Diffuse Arteriolar Disease with Hypertension Group Four, Proc. Staff Meet., Mayo Clin. **14**:210-214 (April 5) 1939; Structural Changes in the Arterioles of the Myocardium in Diffuse Hypertension Group Four, Arch. Int. Med. **66**:579-602 (Sept.) 1940.

25. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1939, p. 653.

PATHOLOGIC CHANGES IN ENDOCRINE GLANDS

Special emphasis has been placed on the possible relationship of endocrine disturbances to hypertension. Raab [26] suggested that three pathogenic factors act alone or in combination to produce vasoconstriction, arteriosclerosis and hypertension. One of these he named the hormonal factor (factor H). It arises from primary corticoadrenotropic hyperactivity of the anterior pituitary lobe and hyperactivity of the adrenal glands. The other two are factors C (cerebral) and R (renal).

The importance of the adrenal gland was illustrated by Perara,[27] who reported a case of hypertension of three years' duration in a 50 year old white man, in whom Addison's disease concurrently developed. The hypertension was maintained during treatment with desoxycorticosterone. When the drug was withheld, the blood pressures fell to normal levels, even though electrolyte and water balance were maintained. The blood pressure promptly rose on administration of the drug. This suggested to Perara that, even though consistent anatomic changes may not be apparent in the adrenal glands, there may yet be an abnormal liberation of certain adrenal cortex hormones concerned in the causation of hypertension.

TABLE 3.—*Pathologic Changes in Endocrine Glands*

Case No.	Adrenals	Thyroid	Hypophysis	Pancreas
1.....	Normal	Normal	.....	Normal
2.....	Normal	Diffuse colloid goiter (small)	Normal	Normal
3.....	Normal	Benign papillary adenoma (small)	.....	Normal
4.....	Focal round cell infiltrations in medulla	Normal	Normal	Normal
5.....	Normal	Normal	Normal	Normal
6.....	Normal	Normal	Necrotic adenoma of anterior lobe	Normal

Reference to table 3 will show that the adrenals were normal in all cases but 1, in which a few small focal collections of mononuclear round cells, resembling lymphocytes, were found in the medulla. This is a common finding in cases without hypertension and no significance is attached to it. In the cortex of one adrenal gland, which, however was not hypertrophied, there were small adenomatous-like arrangements of the cortical cells. However, this has also been seen in patients without hypertension.

26. Raab, W.: Hormonal, Central and Renal Origin of Essential Hypertension: Cerebral and Renal Arteriosclerotic Ischemia as Causal Factors, Ann. Int. Med. **14**:1981-2007 (May) 1941.

27. Perara, G. A.: The Relationship of the Adrenal Cortex to Hypertension, J. A. M. A. **129**:537-538 (Oct. 20) 1945.

The hypophysis was studied histologically in 4 cases. Only one gland (case 6) showed significant pathologic changes. A very small subcapsular adenoma of the anterior lobe had undergone recent necrosis, and its cellular composition was unidentifiable. The major portion of the hypophysis was intact. The patient exhibited body changes suggestive of endocrinopathy.

In 1 case, there was a small benign papillary adenoma of the thyroid isthmus and, in another, a small diffuse colloid goiter was present.

ONSET OF PSYCHOSIS

One of the striking facts brought to light in this study was that related to the duration of time elapsing between the onset of the patient's hypertensive symptoms and the appearance of more or less persistent psychotic behavior. Transient psychotic episodes and purely neurologic manifestations related to episodic cerebral lesions were not included. It was

TABLE 4.—*Relationship of Psychosis to Duration of Illness*

	Appearance of Psychosis	
Case No.	Years After Onset	Years Before Death
1	19	1
2	26	5
3	3	3½
4	9½	½
5	4	2
6	..	10/12

only when the patient began to exhibit more or less constant evidence of mental deterioration, leading to committment to a hospital for mental diseases that the onset of psychosis was recorded.

Table 4 illustrates how late in the course of the disease psychosis may appear. For example, in case 1 the patient had frequent periods of restlessness, irritability, dizziness and overtalkativeness for ten years before mental deterioration set in following a new cerebrovascular incident. In case 2 the patient had repeated strokes resulting in transient hemiplegia, unconsciousness and mental confusion, but only after twenty-six years did he begin to show "organic" signs of mental deterioration.

The rapid downhill course in case 6 may be ascribed to the suppurative infection of the kidneys and the involvement of the pituitary gland. Clinically, the disease was ushered in by mental and neurologic symptoms, although it is possible that a subacute glomerulonephritis may have been present at that time.

An interesting clinical feature present in the majority of cases was the history of spontaneous remissions of neurologic and even mental

symptoms. One patient (case 3) with severe headaches, blurring of vision, depression and paranoid tendencies had remarkable clearing after six weeks' rest in bed. A relapse two years later was again followed by improvement, but by this time permanent cerebral damage had occurred and outstanding neurologic and psychiatric residues remained. This patient died suddenly after a massive cerebral hemorrhage.

Another patient (case 4) for many years had had recurrent cerebrovascular episodes which led to almost complete mental deterioration and blindness. He was disoriented and hallucinated freely, but with continued rest he made such a rapid and startling recovery that he was about to be discharged from the hospital when a sudden massive cerebral hemorrhage caused his death.

PATHOGENESIS

The factors common to all the cases reported here are hypertension, vasospasm, arteriolar sclerosis (cerebral and renal chiefly) and cerebral ischemia and edema. What causes hypertension and what induces vasospasm are questions that have stimulated a great amount of investigation in many branches of medicine, including psychiatry and psychoanalysis, with valuable contributions from each field.

Vasospasm.—According to Fishberg,[25] hypertension is caused by widespread vasospasm. The cerebral arterioles and capillaries, however, are provided with vasoconstrictor nerves which are only about one tenth as effective in the pia as the vasoconstrictor nerves in the skin (Forbes, and Cobb[28]). Cerebral arterioles with sclerotic plaques are particularly hypersensitive to localized vasomotor stimuli (Kennedy, Wortis and Wortis[29]). Thus a defective adaptation of the cerebral capillaries and arterioles would be apt to result from the sudden elevations in the arterial pressure characterizing this disease. Vasoconstriction of the cerebral vessels results from hypertensive stretching of the muscular coat, but portions of the arterioles with walls weakened by lipid degeneration would not be able to contract as vigorously as the better preserved adjoining segments. Consequently, a ballooning out of the vessel into an aneurysmal-like dilatation ensues. At first there would be an exudation of fluid and red blood cells. Finally thrombosis would occur. In some instances the thrombosed vessel is recanalized and

28. Forbes, H. S., and Cobb, S. C.: Vasomotor Control of Cerebral Vessels, in Cobb, S., and Frantz, A.: The Circulation of the Brain and Spinal Cord: A Symposium on Blood Supply, Baltimore, Williams & Wilkins Company, 1938, pp. 201-217.

29. Kennedy, F.; Wortis, S. B., and Wortis, H.: The Clinical Evidence for Cerebral Vasomotor Changes, in Cobb, S., and Frantz, A.: The Circulation of Brain and Spinal Cord: A Symposium on Blood Supply, Baltimore, Williams & Wilkins Company, 1938, pp. 670-681.

provides the site for later hemorrhages and localized exudations of plasma into the adjacent nerve structures.

Another mechanism for the production of localized vasospasm is explained on the basis of hemorrhages into the vascularized intimas of sclerotic arterioles.[17] These hemorrhages may cause not only localized arterial spasms but arteriolar and capillary thromboses as well. The marked degree of medial hypertrophy so frequently seen in the cerebral arterioles is interpreted as anatomic evidence that the normal effect of vasoconstriction has been aggravated, generalized and made more permanent.[5]

Other factors inducing angiospasm may be hormonal, accompanied with hyperactivity of the pituitary and adrenal glands or hypothalamic stimulation. Sudden attacks of hypertension may be the result of hypothalamic excitation (Miller [30]). Some authors have attributed attacks of hypertension to increased vasomotor tonus and irritability resulting from arteriosclerotic ischemia and acidification of the cerebromedullary centers (Raab,[31] and Bordley and Baker [32]). However, neither Cutler [33] nor Tuthill [34] was able to find any significant lesions in the blood vessels supplying the areas in question, nor were any present in our series of cases.

The role of the renal pressor substance elaborated by the ischemic kidney is well known. In the majority of cases, regardless of the initial cause of the hypertension, the renal factor assumes a progressively important part in intensifying and perpetuating it at high levels. In the early stages, however, the question still remains as to whether the ischemic brain, like the ischemic kidney, may not elaborate a humoral pressor substance, for, as Ricker [35] pointed out, the brain alone parallels the kidney in its reaction to arteriosclerosis.

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30. Miller, H. R.: Central Autonomic Regulations in Health and Disease, New York, Grune & Stratton, Inc., 1942.

31. Raab, W.: Central Vasomotor Irritability: Contribution to Problem of Essential Hypertension, Arch. Int. Med. **47**:727-758 (May) 1931.

32. Bordley, J. F., and Baker, B. M.: A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension: A Preliminary Report, Bull. Johns Hopkins Hosp. **38**:320-321 (April) 1926; Arteriosclerosis of the Cerebral Vessels and Pathogenesis of Hypertension, ibid. **39**:229-264 (Oct.) 1936.

33. Cutler, O. I.: Relation of Arteriosclerosis of the Cerebral Vessels to Hypertension: Distribution of Arteries Supplying Pons and Medulla, Arch. Path. **5**:365-379 (March) 1928.

34. Tuthill, C. R.: Hypertension in Relation to the Blood Vessels of the Medulla Oblongata, Arch. Path. **11**:760-765 (May) 1931.

35. Ricker, G.: Sklerose und Hypertonie der innervierten arterien, Berlin, Julius Springer, 1927; cited by Cobb and Blair, in Cowdry, E .V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933, pp. 397-425.

An interesting phase of this problem was opened by the investigations of the psychiatrists and psychoanalysts. Alexander [36] expressed the belief that essential hypertension may develop in persons unable to rid themselves of pent-up hostile impulses through neurotic outlets. This theory received support in the reports of Draper [37] and Riemer,[38] who found that in certain types of hypertension the blood pressures returned to normal when the patients were able to drain off their strongly suppressed anxieties, hostility and feelings of guilt through the development of certain neurotic symptoms. In an interesting analysis of the personalities of patients with arterial hypertension, Binger and his co-workers [39] came to the conclusion that the disorders of personality and the "constitutional vasomotor instability that characterise these people, may only be different aspects of the same fundamental pathologic process."

Cerebral Arteriolar Sclerosis and Ischemia.—There is strong evidence that sclerosis of the arterioles of the brain and the attendant ischemic changes play an important part in the pathogenesis of this type of hypertension. The disparity in some cases between the advanced stages of arteriolar sclerosis in the brain and the relatively mild changes in the renal arterioles is sometimes very striking. There have been a few reports of essential hypertension of many years' duration in which advanced cerebrovascular pathologic change was found in the absence of notable renal vascular disease (Riebold,[40] Davison and Brill [7] and Bordley and Baker [32]).

In this connection, several reports describing cerebrovascular (arteriolar) sclerosis in sickle cell anemia are of considerable interest. In 1939, Bridgers [41] reported the case of a 4 year old Negro child with sickle cell anemia, who at the time she was first admitted to the hospital had a blood pressure of 105 systolic and 65 diastolic. Three and one-half years later, just before she died after a catastrophic cerebral accident, her blood pressure had risen to 150 systolic and 100 diastolic. Autopsy findings revealed extremely severe changes in the cerebral arterioles

36. Alexander, F.: Emotional Factors in Essential Hypertension, Psychosom. Med. **1**:173-179 (Jan.) 1939.

37. Draper, G.: The Common Denominator of Disease, Am. J. M. Sc. **190**:545, 1935.

38. Riemer, M. D.: Psychoses Associated with Essential Hypertension, Psychiat. Quart. **15**:284-295 (April) 1941.

39. Binger, C. A. L.; Ackerman, N. W.; Cohn, A. E.; Schroeder, H. A., and Steele, S. M.: Personality in Arterial Hypertension, New York, Robert Brunner, 1945.

40. Riebold, G.: Dauernde erhebliche Blutdrucksteigerung als Frühsymptom einer Gehirnarterosklerose, München. med. Wchnschr. **64**:1390, 1917; cited by Raab.[26]

41. Bridgers, W. H.: Cerebral Vascular Disease Accompanying Sickle Cell Anemia, Am. J. Path. **15**:353-361 (May) 1939.

consisting of endarteritis obliterans and advanced degrees of hyaline and proliferative fibroblastic sclerosis of the arterioles. Some of the large vessels were also completely obliterated. On the other hand, the renal arterioles were not significantly altered. A second case included in the same report was that of a 62 year old Negro woman with sickle cell anemia. She had a marked degree of hypotension pressure, 80 systolic and 60 diastolic, but in this instance there were no sclerotic or endarteritic changes in the brain. Two more cases of sickle cell anemia characterized by cerebral arteriolar sclerosis and hypertension were later reported by Wertham, Mitchell and Angrist.[42]

CONCLUSIONS

Personal observations of the clinical behavior of patients with recurrent hypertensive cerebral thromboses, coupled with the anatomic evidence presented in 6 cases, indicate that vasospasm and hypertension are the primary factors in the pathogenesis of the disease. The personality structure and constitutional factors related to neurogenic vascular controls are frequently of such a nature as to render the patient particularly susceptible to trigger reactions to emotional stimuli. Marked fluctuations of blood pressure ensue, and the mechanisms of arteriolar vasoconstriction, secondary dilation and thrombosis described by Fishberg [25] are then set into motion.

In the early stages of the disease, the recurrent attacks of vasospasm may result only in localized cerebral ischemia and edema. Consequently, the damage to the brain tissue is temporary and reversible. Symptomatology fluctuates accordingly. The repeated attacks of vasoconstriction lay the groundwork for the later development of arteriolar sclerotic changes. These consist in medial hypertrophy and hyperplasia, fatty degeneration of the intima and media, hyalinization of all three vascular tunics, subintimal vascularization and mural hemorrhages, perivascular extravasations of plasma and red blood cells and thrombosis. These arteriolar sclerotic changes contribute to the cerebral anemia, and thromboses due to angiospasm and stasis in vessels with degenerated fatty walls become more frequent.

With each hypertensive cerebral episode relatively few nerve cells are actually irreversibly damaged. Even in areas about thrombosed vessels or perivascular extravasations of fluid (figs. 1 *A* and 4 *B*), the nerve cells, though compressed and atrophied, are still present and presumably functioning. Initially, however, the area of impaired cerebral function is much larger than the original focus of perivascular necrobiosis. When the edema subsides or the extravasated blood is absorbed, cells which have not been destroyed recover function, partially or completely.

42. Wertham, F.; Mitchell, N., and Angrist, A.: The Brain in Sickle Cell Anemia, Arch. Neurol. & Psychiat. **47**:752-767 (May) 1942.

As the disease process advances, however, more and more arterioles become implicated. Secondary disturbances may occur in the venous circulation. Consequently, widespread lipid degeneration of the nerve cell cytoplasm occurs and the brain reserve is correspondingly diminished to the point that the threshold for the development of psychotic symptoms is reached. Fortunately, in the majority of cases this does not occur until the latter stages of illness and is usually a sign that the end is not far off.

It is important that this syndrome be kept in mind because the diagnosis of brain tumor may be made on the basis of localizing symptoms (Ketterer [43] and Griffith [44]). Conversely, neoplasms of the posterior fossa may simulate recurrent hypertensive cerebral thrombosis (Meyer [45]). Because of the mental symptoms, a patient may be stigmatized with the diagnosis of schizophrenia. On the other hand, schizophrenic patients with hypertension may be given the erroneous diagnosis of recurrent hypertensive cerebral thrombosis. The commonest error in diagnosis is classifying the patients as having psychosis with cerebral arteriosclerosis. Such patients may be relegated to the wards with other arteriosclerotic patients and lost in the shuffle. Occasionally, the diagnosis of dementia paralytica is made, especially if the patient has or has had a positive serologic reaction.

SUMMARY

Recurrent hypertensive cerebral thrombosis is a specific clinicopathologic entity. It is a variant of hypertensive cardiovascular disease in which cerebral symptomatology and cerebral pathology may take precedence or predominate over cardiorenal vascular changes.

A detailed clinicopathologic analysis of 6 cases is presented. The average age of onset was 40 years. Both sexes were affected. The average span of life after the onset of symptoms was 11.4 years, but 1 patient lived for 31 years. The average systolic level of blood pressure was 223 mm. of mercury, and the average diastolic level was 123 mm. of mercury. Persistent major psychotic symptoms tended to occur late in the disease, and their appearance was always a sign of grave prognostic import.

The essential pathologic change resided in the small vessels of the brain, chiefly the arterioles and capillaries. The large cerebral arteries

43. Ketterer, C. H.: Hypertensive Encephalopathy Resembling Brain Tumor, M. Bull. Vet. Admin. **15**:413-414 (April) 1939.

44. Griffith, R. S.: Hypertensive Encephalopathy Simulating Brain Tumor, M. Clin. North. America **17**:827-835 (Nov.) 1933.

45. Meyer, B. C.: Neoplasm of Posterior Fossa Simulating Cerebral Vascular Disease: Report of Five Cases with Reference to Role of Medulla in Production of Arterial Hypertension, Arch. Neurol. & Psychiat. **45**:468-480 (March) 1941.

were rarely extensively affected. Renal arteriolar disease in most cases was less severe than cerebral arteriolar disease. In the majority of cases cardiac lesions were relatively mild.

Examination of the endocrine organs, including the hypophysis, thyroid and adrenal glands and the pancreas, in 5 cases failed to reveal any fundamental changes which could be linked causally with the hypertension. A tiny pituitary adenoma was found in 1 case.

The basic pathogenic mechanisms are considered to be recurrent cerebral vasospasm, progressive arteriolar sclerotic degenerative changes with intramural and perivascular hemorrhages, arteriolar and venular thromboses and cerebral ischemia and edema.

The term recurrent hypertensive cerebral thrombosis is suggested as the proper clinicopathologic designation of this syndrome.

TECHNIC OF CORTICAL EXCISION

An Experimental Study of Postoperative Cicatrization

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THE PROBLEM of cicatrization after cortical excision or incision is one which faces the neurosurgeon constantly, whether the tissue he handles is neoplastic or cicatricial. The recent introduction of surgical procedures such as lobotomy, convolectomy and topectomy for the treatment of neuroses and psychoses has increased the number of surgically produced cicatrices. Since a cerebral cicatrix is a potential epileptogenic lesion, it is important to know what factors enter into its production. Therefore, the following series of experiments were performed to determine which technic of excision produces a better scar from the standpoint of gliosis and tendency to become epileptogenic.

REVIEW OF LITERATURE

Pathology.—Tschistowitsch [1] used a platinum needle to produce stab wounds in brains of dogs and pigeons and studied the brains three to one hundred and thirty days after injury. He concluded that connective tissue elements of pia and blood vessels played the chief role in scar formation. The neuroglia was insignificant and merely aided in forming a sclerotic zone about the cicatrix by shrinking.

Wilson [2] performed blunt needle punctures of the human brain for injection of arsphenamized serum. A connective tissue core replaced the track except in the deeper parts, where a hollow space was found. Reaction was greater in the gray matter than the white, and the neuroglial reaction was minor.

Del Rió-Hortega and Penfield [3] described in detail the changes occurring in neuroglia astrocytes about stab wounds, showing that multiplication begins as early as the fourth day and is followed by formation of fibers and a radial arrangement of the cells. At the center of such tracks a strong connective tissue core was always found.

From the Department of Neurology and Neurosurgery of McGill University and the Montreal Neurological Institute.

1. Tschistowitsch, J.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. Path. **23**:321, 1898.

2. Wilson, R. B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75-84 (Jan.) 1926.

3. del Río-Hortega, P., and Penfield, W.: Cerebral Cicatrix, Bull. J. Hopkins Hosp. **41**:278-303, 1927.

Penfield and Buckley [4] carried this problem nearer to its solution by determining in dogs whether a clean excision of cortex produced less scarring than one in which debris was left behind. They made wounds with a blunt brain needle and with a cannula which removed a cylinder of tissue. They concluded that (1) the two needles cause the same amount of hemorrhage; (2) about the closed tracks the astrocytes send in their expansions concentrically; (3) about open tracks these expansions are tangential; (4) compound granular corpuscles are more numerous around closed tracks than around open ones, and (5) there are, in general, greater formation of adhesions, greater distortion and greater destruction of brain about the tracks made by a closed needle than about the tracks made by an open needle of the same size. It would seem that when injured cerebral tissue is not removed it produces a more serious pathologic condition than when an equal amount of such tissue is cleanly removed.

Linell [5] repeated Penfield and Buckley's experiments with brain punctures. He found that microglia transformed into gitter cells in three days, reaching a maximum in six days. Astrocytes hypertrophied in three days; in six days the change was marked; in two weeks there was a marked increase in number with definite felting of the astrocytic processes. He confirmed Penfield and Buckley's finding that the scarring was proportional to the amount of damaged tissue left behind.

Lear and Harvey [6] concluded that incision or removal of the dura mater without injury to the arachnoid resulted in regeneration of the dura with few superficial adhesions between the two membranes. Injury to the pia-arachnoid, by leaving raw brain exposed, resulted in the formation of a denser adhesion. Injury to the pia-arachnoid broke the barrier formed by avascular arachnoid and necessarily removed the protective covering of the brain. Such a break called forth an energetic connective tissue response, whether the nervous system was exposed in the central or in the peripheral system, as though the nervous tissue itself were indeed a foreign body.

Electroencephalography.—It is generally conceded that injury to nerve tissue causes an alteration of normal rhythm and the appearance of abnormal discharges. This occurs in both man and lower animals.

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4. Penfield, W., and Buckley, R. C.: Punctures of the Brain: The Factors Concerned in Gliosis and in Cicatrical Contraction, Arch. Neurol. & Psychiat. **20**:1-13 (July) 1928.

5. Linell, E. A.: The Histology of Neuroglial Changes Following Cerebral Trauma, Arch. Neurol. & Psychiat. **22**:926-948 (Nov.) 1929.

6. Lear, S., and Harvey, M.: The Regeneration of the Meninges and Pia-Arachnoid, Ann. Surg. **80**:536, 1924.

Kennard [7] and Kennard and Nims [8] studied the effects of cortical excisions with and without combined lesions of the basal ganglia on the electroencephalograms of monkeys. Only when the lesion extended to the basal ganglia did slow waves, sharp waves or spikes appear. However, during the immediate postoperative period these authors recorded ipsilateral depression of voltage potentials, a fact which was attributed to edema of the scalp.

Jasper and Bornstein [9] noted the effect of cortical injury in cats, dogs, monkeys and rabbits. With a fixed electrode in place they studied the effect of contusion and laceration. Simple concussion produced a momentary generalized excitation of the brain which was followed by electroencephalographic evidence of a transient depression in cortical function. Contusion or laceration of the cortex also caused an initial intense local excitation but was followed by much more persistent local alteration of function. These changes were indicated by continuous slow wave discharges which were interrupted by epileptiform spike discharges.

Williams and Denny-Brown [10] investigated the effects of concussive injury. They found in animals that concussion was associated with diminution or cessation of the electrical activity of the whole cerebral hemisphere; delayed appearance of abnormally slow waves seemed to represent a stage in recovery from concussion. Walker, Kollros and Case[11] criticized this work on technical grounds, pointing out that with their method of recording the amplifiers were blocked out for a few seconds after the concussive blow. With this objection removed by their own method of recording, the latter authors found that the initial effect of a concussive blow was excitatory rather than paralytic. The functional depression following concussion was considered by these authors to be caused by a fatigue or extinction phenomenon resulting from intense stimulation.

The investigation of brain injury in human beings apart from that produced by penetrating missiles, acceleration or direct blunt blows is

7. Kennard, M. A.: The Effects on the EEG of Chronic Lesions of the Basal Ganglia, Thalamus and Hypothalamus of Monkeys, J. Neurophysiol. **6**:405-415, 1943.

8. Kennard, M. A., and Nims, L. F.: Effect on the Electroencephalogram of Lesions of Cerebral Cortex and Basal Ganglia in Macaca Mulatta, J. Neurophysiol. **5**:335-348, 1942.

9. Jasper, H. H., and Bornstein, M.: Proceedings Fifth Meeting Association Committee on Army Medical Research (Canada), November 1944, vol. 4, p. 6619.

10. Williams, D., and Denny-Brown, D.: The Cerebral Changes in Experimental Concussion, Brain **64**:223, 1941.

11. Walker, A. E.; Kollross, J. J., and Case, T. J.: The Physiological Basis of Concussion, J. Neurosurg. **1**:103-115, 1944.

very meager. Cohn [12] reviewed the postoperative electroencephalograms of 30 patients on whom prefrontal lobotomy had been done. All showed 2 to 5 per second slow waves from the frontal leads. He expressed the belief that there was no correlation between the slow wave activity and the injury to the caudate nucleus.

Jasper, Kershman and Elvidge [13] reviewed the electroencephalograms of patients with acute head injuries. The tracings were characterized by irregularities, reduction or complete disappearance of normal cortical rhythms, appearance of delta waves at frequencies of 1 to 7 per second and production of excitatory changes in the form of rapid rhythms, spikes and sharp waves. The clinical severity of injury was closely related to the severity of the electroencephalographic changes.

Williams [14] examined the electroencephalograms of 74 patients with acute head injuries and noted widespread abnormality in the form of suppression of normal waves and appearance of slow waves. The severity of the changes was proportional to the severity of injury and the clinical state, and clinical improvement paralleled the electroencephalographic improvement. Williams and Reynell [15] reported on 90 consecutive electroencephalograms of patients with gunshot wounds of the head on D-Day. The records showed a silent area in 30 per cent; focal slow waves in 55 per cent, and generalized abnormality in 13 per cent; 19 per cent were normal. It was common for these authors to find only suppression of activity after removal of contused tissue. Forty-six patients with such suppression were studied. In 83 per cent there was complete and permanent destruction of tissue, and in 17 per cent there was only local contusion causing a temporary suppression. These authors noted that suppression of normal rhythms occurred independently of slow wave activity.

MATERIALS AND METHODS

Three methods of excising cortex were used: 1. A block of cortex approximately 5 by 15 mm. was removed with the cutting cautery to a depth of 3 to 4 mm. 2. A similar block was outlined by placing sutures in the cortex; when tied, these sutures cut the brain cleanly as well as gathered the blood vessels in one group. The block of cortex was then lifted out with a blunt dissector. 3. A gyrus was removed by suction, leaving the surrounding cortex covered with its normal investment of pia-arachnoid and blood vessels.

12. Cohn, R.: Electroencephalographic Study of Prefrontal Lobotomy, Arch. Neurol. & Psychiat. **53**:283 (April) 1945.

13. Jasper, H. H.; Kershman, J., and Elvidge, A. R.: Electroencephalography in Head Injury, A. Research Nerv. & Ment. Dis. Proc. **15**:388, 1943.

14. Williams, D.: The Electroencephalogram in Acute Head Injuries, J. Neurol. & Psychiat. **4**:107, 1941.

15. Williams, D., and Reynell, J.: Abnormal Suppression of Cortical Frequencies, Brain **68**:123-161, 1945.

Three cats and 4 monkeys were used for each procedure. All excisions were approximately the same size and in the same location. In cats all lesions were in the suprasylvian gyrus; in monkeys the postcentral gyrus was removed. None of the lesions were deep enough to touch the basal nuclei. Bleeding was controlled with tantalum clips or by gentle pressure with moist cotton. Control experiments were performed in an equal number of separate animals by making a deliberate injury without any attempt to remove contused tissue. The dura was closed tightly. In cats the bone removed for exposure was discarded; in monkeys the bone flap was wired back in place. No wound infection occurred.

Preoperative and postoperative electroencephalograms were taken, using bipolar recordings with a phase reversal setup on an Offner machine. Phonograph needles tapped gently into the skull were used instead of scalp electrodes; the needles were coated to the tip with plastic material (vinylite) to insulate against muscle potential artefact. The electroencephalograms of the monkeys were taken without anesthesia. The cats were lightly anesthetized with thiopental sodium (pentothal sodium®)—0.5 grain (0.03 Gm.) per kilogram of body weight given intraperitoneally.

In the monkeys the preoperative and postoperative thresholds to a metrazol® (pentamethylenetetrazol) seizure were determined. A 10 per cent solution was given intravenously in increasing doses until a convulsion was produced. The postoperative thresholds were tested twelve to fifteen months after operation. The amount of metrazol® was divided by the weight of the animal in kilograms to determine the amount per kilogram of body weight.

The brains were fixed in situ by injection[16] of a mixture of 4 per cent formaldehyde solution and acacia into the carotid artery. The bone was rongeured away and the brain removed with the dura attached. Hematoxylin and eosin, hematoxylin and Van Gieson stain and Cajal's gold chloride-mercury bichloride method for astrocytes were used for staining.

RESULTS

1. *Cats.*—Electroencephalograms of the Suction Removal Group: Three cats were used and followed for thirty-two days, eighteen months and two and one-half months. None of the recordings showed any abnormality except for depression of activity over the area of excision for the first two weeks after operation. No seizures occurred.

Electroencephalograms of the Thread Removal Group: Three cats were followed for four, fourteen and sixteen months. The same electroencephalographic findings were obtained as in the suction removal group, and no seizures occurred.

Electroencephalograms of Cautery Removal Group: Three cats were followed for fourteen, fifteen and seventeen months. The electrographic findings were the same as in the other two groups. None of the animals had seizures.

Electroencephalograms of the Injury Group: Two cats were followed for two and fifteen months. Again no abnormality was recorded

16. Windle, W. F.: Water Content of Brain After Experimental Concussion and Its Noncontributory Relation to Histopathology of Concussion, J. Neurosurg. **3**:157-164, 1946.

except for depression of activity. In 1 animal the scar was exposed under local and thiopental sodium (pentothal sodium®) anesthesia, and again neither slow waves nor spike activity could be found. The depression of activity was recorded over the entire hemisphere as well as the scarred area.

Gross Observations in Cats: The brains from the group which had suction removals (fig. 1) looked more normal than those in which tissue was removed with cautery or thread; the pia was intact along the excision edges, and the two convolutions had come together, leaving no superficial cyst. The meningocerebral scar in the thread group was

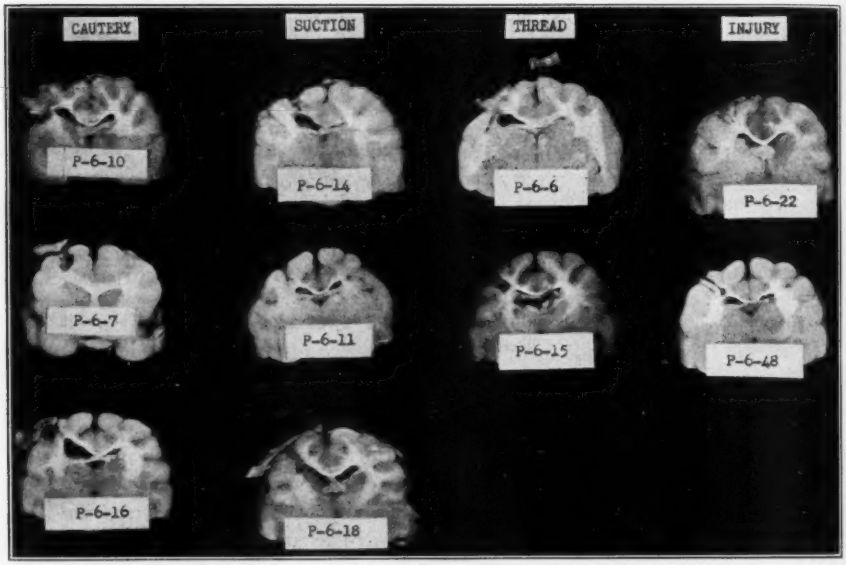

Fig. 1.—Brains of cats. The area operated on is at the upper left. The suction removal group shows less scarring than any other group. The worst scars are in the cautery removal and injury groups, while those of the thread removal group are intermediate.

more fibrous than in the suction group. The brains in the injury and cautery groups looked worst of all.

Microscopic Observations in the Suction Removal Group: The gyrus had been removed cleanly, and the opposing pial edges had become approximated (fig. 3). The pia was intact and had prevented ingrowth of connective tissue. There was gliosis in the exposed white matter but not in the gray.

Microscopic Observations in the Thread Removal Group: The gyri had been cut across at the crest of the convolution (fig. 3), and

dense meningocerebral adhesions had formed. In several places the connective tissue had invaded the cerebral tissue and mingled with the glial scar.

Microscopic Observations in the Cautery Removal Group: The conditions observed were similar to those in the thread removal group (fig. 3) except that the scar was denser.

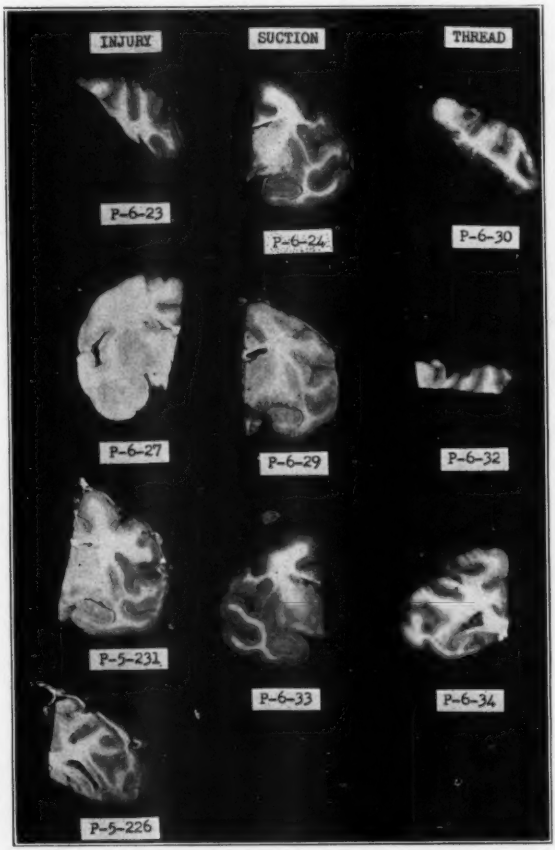

Fig. 2.—Brains of monkeys. The gross appearance is similar to that of the cats. No cautery excisions were done on these animals.

Microscopic Observations in the Injury Group: At the place of injury there was marked piloid gliosis with the astrocyte fibers being oriented perpendicular to the dura (fig. 3). There was a connective tissue core in the center of the scar.

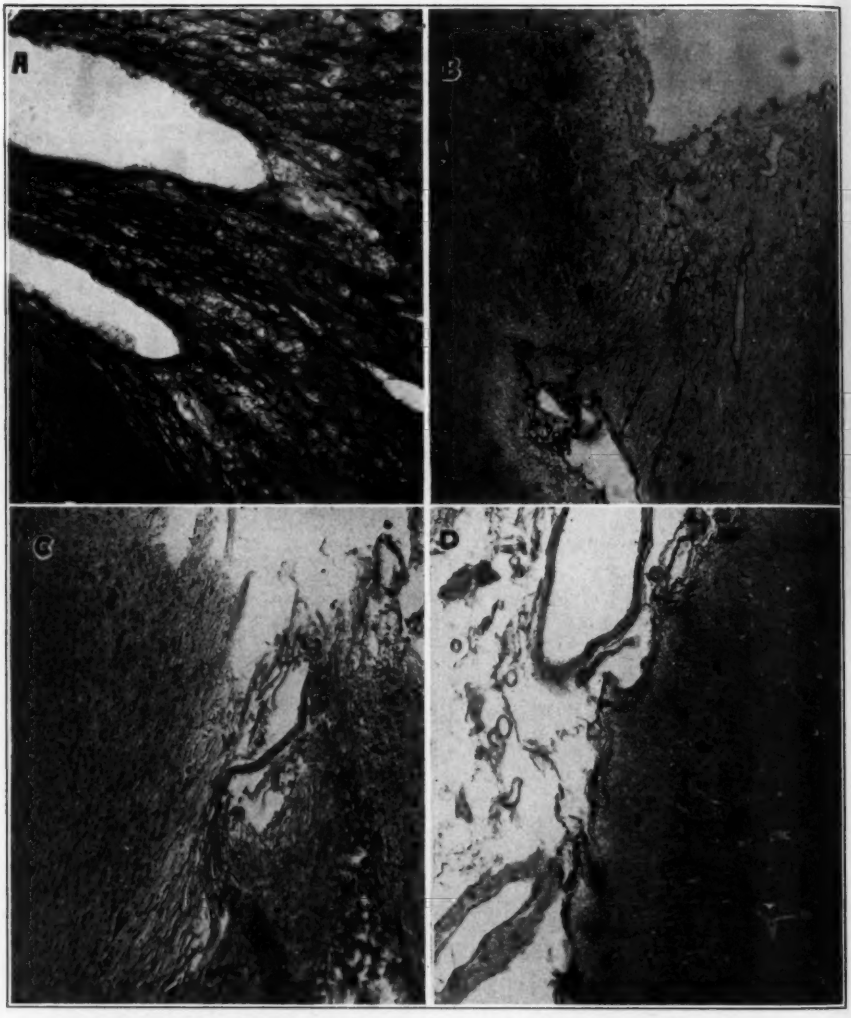

Fig. 3.—Photomicrographs of scars of cats. *A*, injury group. There is severe piloid gliosis. A connective tissue core is in the center. Gold chloride–mercury bichloride, stain; × 90. *B*, thread excision group. The pia is not intact. There are increased vascularity and connective tissue invasion. Moderate gliosis is present. Hematoxylin and Van Gieson stain; × 90. *C*, cautery excision group. The pia is not intact, and there is marked gliosis. Hematoxylin and Van Gieson stain; × 90. *D*, bank of subpial resection. There is no gliosis in the gray matter, and the pia is intact. Hematoxylin and Van Gieson stain; × 90.

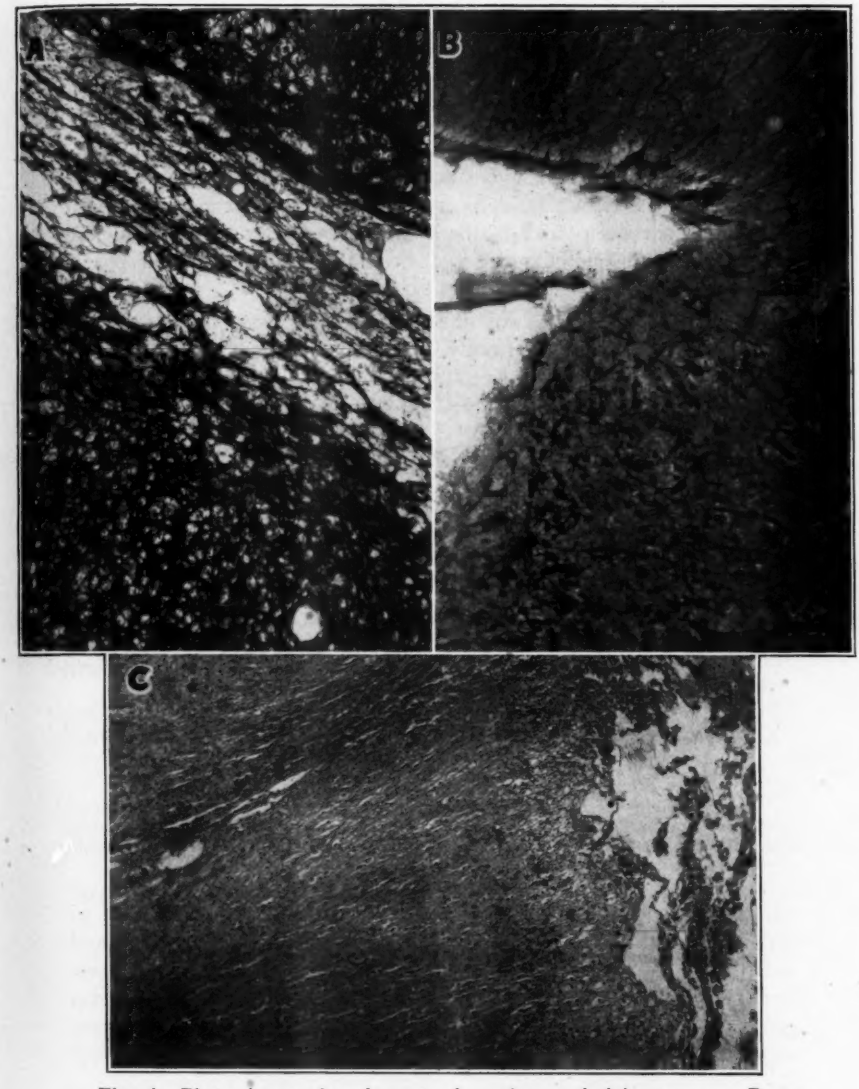

Fig. 4.—Photomicrographs of scars of monkeys. *A*, injury group. Dense piloid gliosis is present. Gold chloride–mercury bichloride stain; × 98. *B*, subpial resection group. There is proliferation of astrocytes in the white matter (below) but not in the gray matter (above). Gold chloride–mercury bichloride stain; × 98. *C*, thread excision group. There is moderate gliosis in the gray matter, as well as inflammatory cells in the meninges. Hematoxylin and Van Gieson stain; × 98.

2. *Monkeys.*—Electroencephalograms of the Suction Removal Group: Four monkeys were followed for fifteen, seventeen, seventeen and twenty-three months postoperatively. The electroencephalogram (fig. 5) during the first few days showed marked depression of amplitude of normal activity over the area of excision with many slow waves and an occasional sharp wave. The depression was then supplanted by slow and sharp waves over the area of excision and multiple spike discharges from the homologous area in the opposite hemisphere occurring independently of the side operated on. This abnormality persisted as long as six weeks in 2 of the monkeys, but after that it gradually subsided. At the end of twelve to eighteen months the electroencephalograms were normal. No seizures occurred.

Electroencephalograms of the Thread Excision Group: Four monkeys were studied for twenty, twenty, twenty-two and twenty-one

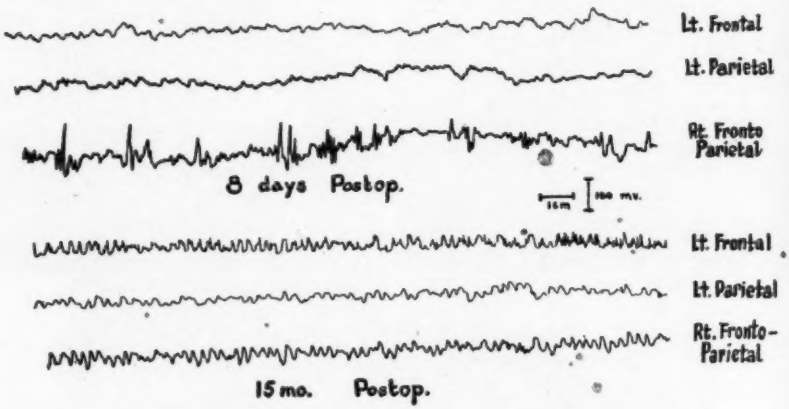

Fig. 5.—Eight days after operation there are random slow waves and depression of voltage on the side of operation (left) and multiple spikes from the intact side. After fifteen months the record is normal. Note the return of the alpha rhythm in the lower record.

months postoperatively. The tracings (fig. 6) showed depression of activity over the area of excision as well as a few random slow and sharp waves during the first month. The abnormality in the early postoperative period was not so marked as in the suction removal group. After one month the records were normal except for an occasional slow wave and slight depression of activity. At the end of twelve to eighteen months all records were normal and none of the animals had fits.

Electroencephalograms of the Injury Group: Four monkeys were followed for three, eleven, nineteen and twenty months. There was immediate suppression of normal rhythms over the area of excision as well as the whole hemisphere (fig. 7). This lasted for several weeks.

High amplitude spikes and sharp waves appeared within forty-eight to seventy-two hours and persisted for at least two months. Some of these were transmitted to the opposite side. At times the side of injury showed depression of activity and the opposite side showed

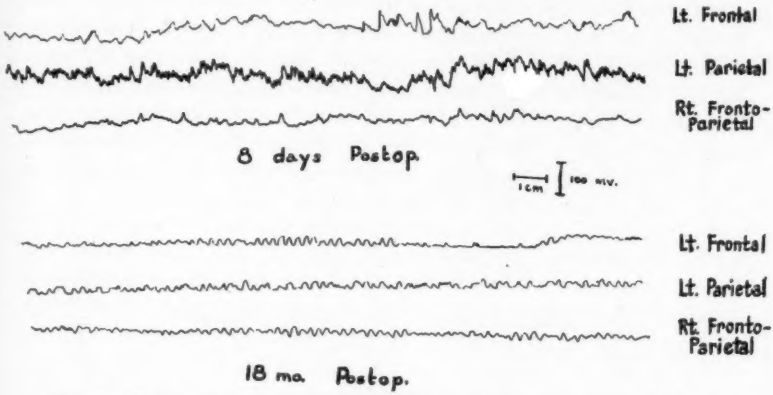

Fig. 6.—Eight days after operation there are random slow waves and a few sharp waves reversing on the side of operation (left). After eighteen months the record is normal and the alpha rhythm well developed.

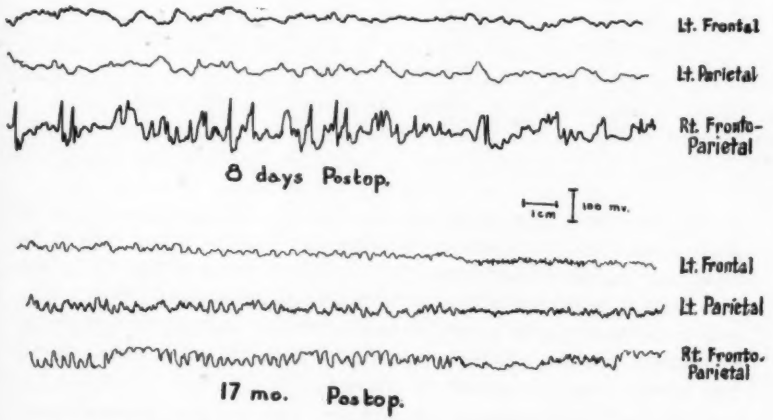

Fig. 7.—Eight days after operation there are random slow waves and a few sharp waves reversing on the side of operation (left) as well as depression of voltage. The intact side shows multiple spike discharges. After seventeen months the record has returned to normal with a well developed alpha rhythm.

sharp waves and occasional spikes. The tracings returned to normal in eighteen months. No fits occurred.

Gross Observations in Monkeys: The convolutions in the suction removal group (fig. 2) had come together, leaving hardly any external

evidence of operation; there were a few delicate meningocerebral adhesions. The thread removal group showed marked meningocerebral adhesions with roughness and unevenness of the excision edges. The injury group was worst of all.

Microscopic Observations in the Suction Removal Group: The excised gyrus had been removed cleanly, leaving a tuft of white matter at the bottom. The edges of cortex had come together (fig. 4) without any superficial cyst formation. A few meningocerebral adhesions, as well as minimal thickening of the pia-arachnoid, were present. The astrocytes in the white matter showed proliferation, but those in the adjacent gray matter appeared normal except for slight proliferation of the subpial astrocytes. The neurons were well preserved.

Metrazol® Data

Monkey No.	Preoperative Weight, Kg.	Preoperative Dose of "Metrazol," Cc.	Dose per Kilogram, Cc.	Postoperative Weight, Kg.	Postoperative Dose of "Metrazol," Cc.	Dose per Kilogram, Cc.	Reduction, Percentage	Average Reduction, Percentage
Injury Group								
23	3.35	0.43	0.13	5.5	0.25	0.04	70	
27	3.2	0.41	0.13	5.5	0.25	0.04	70	
								70
Suction Removal Group								
27	3.05	0.50	0.16	4.2	0.35	0.08	50	
28	3.4	0.47	0.14	4.5	0.35	0.08	43	
29	2.4	0.38	0.16	3.8	0.38	0.10	38	
33	2.75	0.35	0.13	3.8	0.35	0.09	31	
								40
Thread Removal Group								
30	3.75	0.60	0.16	6.8	0.55	0.08	50	
31	3.5	0.45	0.13	5.0	0.30	0.06	55	
32	3.3	0.42	0.13	6.4	0.40	0.06	55	
34	3.8	0.38	0.10	5.5	0.35	0.06	40	
								50

Microscopic Observations in the Thread Removal Group: The white matter had come up to the dura and become united with it by a firm meningocerebral cicatrix (fig. 4). The connective tissue response was marked and invaded the cerebral tissue in several places. The astrocytes were greatly increased in number and both piloid and plump forms were present. The gliosis involved both gray and white matter. The neurons were decreased in number.

Metrazol® Thresholds in Monkeys: The seizure threshold was studied to determine whether the scars produced by the different methods of removal would lower the threshold or produce a potentially epileptogenic lesion. None of the seizures produced by metrazol® were focal in either convulsive movements or electroencephalographic discharge. The brain injury group of 2 monkeys showed a reduction in the convulsive threshold postoperatively as compared with preoperatively of 70 per cent (the table) whereas in the suction and

the thread removal group the thresholds were reduced by 40 and 50 per cent respectively. The difference of 10 per cent is not necessarily of statistical importance, but the differences of the excision groups from the injury group of 20 and 30 per cent would seem to indicate that injury will reduce the seizure threshold more than does cortical excision. Metrazol® was also given intramuscularly to the monkeys at varying times after operation to activate the electrical discharges from the region of the scars. If abnormality was present, it could be accentuated and made sharper, but if the resting electroencephalogram was normal no latent abnormality could be activated.

COMMENT AND SUMMARY

In the cats the postoperative electroencephalograms did not indicate any difference in the tracings between suction, cautery and thread removals; in fact, the electroencephalograms of the injury group were no different from others because all the animals showed only depression of electroactivity over the area of operation. The explanation for the depression of cortical electroactivity and lack of abnormal discharges in the form of slow and sharp waves is obscure. Evidently the proper stimulus for abnormal discharges was lacking.

In monkeys the lacerating brain injuries produced the most immediate and profound electroencephalographic change consisting in slow waves, sharp waves and spikes as well as depression of voltage and suppression of normal rhythms on the side of operation. The abnormality produced by cortical excision was much less than that produced by injury; the electroencephalographic changes in the first few weeks after operation were more pronounced in the suction group than in the thread group. However, after a year all records had returned to normal, including those of the injury group. The most abnormal tracings did not appear on the first postoperative day but began about three days later, reaching a maximum in seven to eight days. This may indicate that cerebral edema was partly responsible for the abnormality. After twelve to eighteen months no great difference between thresholds to metrazol® of the different groups could be obtained, but all showed a reduction compared with the preoperative threshold, the greatest being the injury group.

The suction and injury removals in monkeys produced marked abnormality in the electroencephalogram within the first six to eight weeks, not only on the ipsilateral but also on the contralateral side. All these changes were definitely shown to be reversible, indicating that spontaneous regression of abnormal discharges, even of marked severity, can occur. Why none of these lesions became epileptogenic is difficult to explain. During the removal by suction, some sort of injury, the effects of which were also reversible, was produced. Why this did not also occur in the thread removal group is not known.

Depression of amplitude of discharges compared with those of the opposite side may indicate that this is a primary type of reaction to injury in addition to production of sharp and slow waves. It was certainly not an artefact caused by edema of the scalp, because the electrodes were driven into the skull itself. It was not caused by an error of amplification, because recalibration of the machine as well as reversal of the amplifiers caused no change in the record. That it was not caused by extensive removal of brain tissue is shown by the fact that the area left by removal was quickly filled in by the edges of the excision, as seen by direct inspection of the area operated on in animals which died early in the postoperative period. Furthermore, the depression involved the whole hemisphere, which might indicate that a suppressor area was involved.

The pathologic examination of both monkeys and cats showed that the worst scars were produced by injury. The best ones from the standpoint of scarring were those made by suction removal. In the last group the pia provided an effective barrier to the invasion by connective tissue.

CONCLUSIONS

1. Better scars as judged by the amount of gliosis were produced by suction removal than by thread excision.

2. The electroencephalograms of the suction removal group were worse than those of the thread removal group in the immediate postoperative period, but after twelve to eighteen months none of the electroencephalograms of animals which had undergone either cortical excision or injury was abnormal.

3. Since none of the animals had seizures, no conclusion can be drawn concerning the tendency to produce an epileptogenic lesion by different types of removal.

4. Some of the scars were grossly and microscopically similar to those producing epilepsy in human beings, but there is no histologic difference to explain why they did not produce epilepsy in animals.

LATE CHANGES IN THE BRAIN STEM FOLLOWING TRIGEMINAL TRACTOTOMY

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THIS paper is concerned with the description of a brain stem that was obtained nine months after section of the trigeminal tract had been made in the medulla oblongata, following the method suggested by Sjöqvist.[1]

No other description of a similar case can be found in the literature, and the requisite conditions for scientific inquiry were satisfactory. The patient was a reliable witness, and it was possible to record the postoperative objective sensory changes with reasonable precision. The operation technically was satisfactory. The specimen was obtained nine months after the operation, and thus any degenerative changes that were likely to occur would have been completed. The specimen was obtained within a few hours after death, and so the postmortem changes were minimal.

REPORT OF A CASE

A man aged 43 had for one year suffered from continuous pain in the left side of his face that could not be accounted for by demonstrable lesion in the tissues of the face, in the central nervous system or anywhere else in the body. The characteristics of the pain were that it was continuous, had a burning quality and was not made worse by local pressure. Indeed, the man was constantly pressing on his jaw with his finger in an effort to get relief. Though the main pain was continuous, there were occasionally sharp twinges that were difficult to localize.

From experience it is well known that pain such as this is not relieved by trigeminal sensory root section. Indeed, the patient's burden is often increased because not only is he left with his pain but he now experiences the unpleasant sensation of numbness.

Tractotomy was performed, and it was satisfactory as judged by the postoperative objective sensory loss which will be described briefly later. No relief

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Dr. Erskine is from the School of Anatomy, University of Dublin, Trinity College. The technical work for this paper was done while he was a member of the staff of the Department of Anatomy, St. Mary's Hospital Medical School, London, England.

1. Sjöqvist, O.: Studies on Pain Conduction in Trigeminal Nerve, Acta psychiat. et neurol., 1938, supp. 17, pp. 1-139.

from pain was obtained. Purely from the clinical point of view, two problems were to be resolved in this case. The first one was what the true nature of the underlying lesion might be that was causing the pain. The second was why an apparently successful tractotomy had failed to relieve the pain. Also there were several purely neuroanatomic problems involved, and these will be discussed later.

Postoperative Findings.—1. Pain: The sensation of pinprick was lost in all three divisions of the left trigeminal nerve (fig. 1). The cornea was analgesic, but sensation to light touch remained. Deep pressure pain in the face was present.

2. Thermal Sense: There was marked distortion of thermal sense in the whole of the trigeminal field on the side on which operation was done.

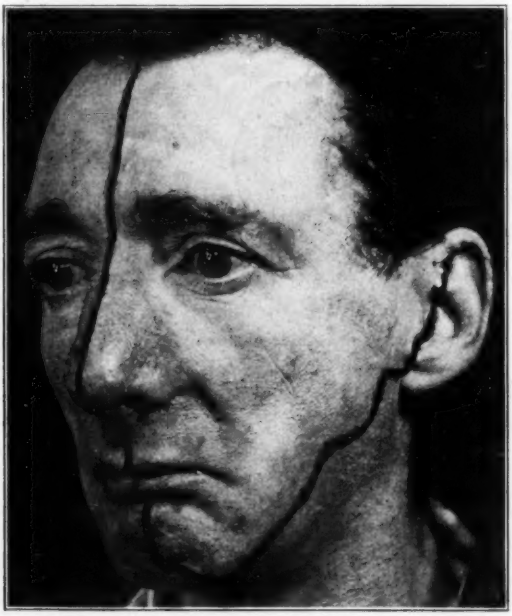

Fig. 1.—Clinical photograph showing the area in which postoperative sensory changes occurred.

3. Light Touch: No absolute loss occurred in this modality of sensation, but, on the other hand, there was some kind of deterioration. In particular, when the face was touched over a broad area the sensation experienced was lighter than that on the untreated side. In the von Frey hair test only 8 stimuli out of 10 as compared with the opposite side were registered.

4. Taste: Sensation of taste was not lost on the analgesic side, but the speed at which discrimination was carried out was decreased.

5. Incoordination: For ten days after operation there was a coarse nystagmus on fixation of the eyes to the left. Also there was marked impairment of body balance with a tendency to fall backward, and this disability lasted for many

weeks. There was good control of the movements of the muscles of the tongue, of the face and of the throat.

MATERIAL AND METHODS

The specimen was about 6.5 cm. long and consisted of the medulla oblongata, pons and part of the midbrain. It had been mordanted for myelin staining and embedded in pyroxylin by Dr. Pollock, of Manchester, England. Serial sections were now made, the majority being cut at 20 microns. Every tenth section was stained for myelin by the Weigert-Kultschitzky method. A few selected sections were stained with cresyl violet and by a modification of the Marchi technic.

CHANGES IN THE TRIGEMINAL SYSTEM

The sections from the lowest part of the specimen were taken through the caudal end of the medulla oblongata at its junction with the spinal cord (fig. 2 *a*).

Spinal Tract of the Trigeminal Nerve.—The spinal tract of the trigeminal nerve showed marked degeneration. A shallow sulcus had developed on the surface of the medulla oblongata over the site of the tract and was visible in these sections. There were a number of intact, finely medullated fibers, almost all in the dorsal part of the area of the tract (fig. 2 *b*); in number they were less than 2 per cent of those on the opposite side. It was difficult to distinguish the exact number of fibers which belonged to the spinal trigeminal tract, since it is probable that some of them were afferents and collaterals of the dorsal nerve roots; these appeared in caudal sections cut longitudinally at the dorsal and medial side of the trigeminal nucleus. Between 60 and 80 fibers of the descending trigeminal tract were present here. The much larger and more heavily myelinated fibers of the dorsal spinocerebellar tract were sharply outlined ventrolateral to the region of the spinal tract of the trigeminal nerve; they did not seem to have encroached to any extent on the area of this tract.

Higher sections (fig. 3 *a*) at the level of the upper limit of the pyramidal decussation showed substantially the same conditions in respect to the spinal trigeminal tract; the proportion of fibers in relation to the intact side was about the same, and since these levels were above the afferents of the cervical dorsal nerve roots they showed that a number (about 80 to 100) of descending trigeminal tract fibers were intact (fig. 3 *b*).

Spinal Tract of the Trigeminal Nerve at the Site of the Incision: Sections at this point showed that the level of the incision was just below the midolive region (fig. 4 *a*). The fibers of the spinal trigeminal tract appeared to be almost completely interrupted (fig. 4 *b*). Two small clear areas lay close to each other in the section nearest the center of the site of incision, which extended through about a dozen sections. The clear areas probably represented small foci of gliosis with

cyst formation. The larger were about 0.5 mm. in diameter and the smaller about 0.1 mm. On the lateral side of the spinal trigeminal tract there was included in the operative incision a layer 1 to 1.5 mm. thick of the fibers of the dorsal spinocerebellar tract, which pass up to take part in the formation of the restiform body.

a

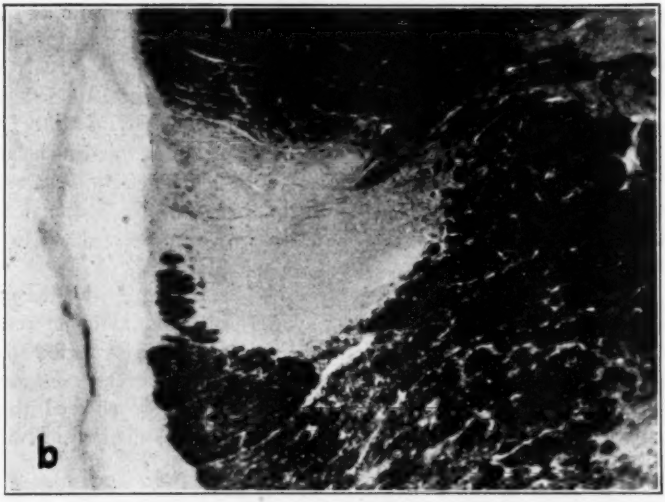

Fig. 2.—(*a*) Drawing to show the level of the section (*b*) which was taken at the lower end of the specimen. On the left side is shown the formation of a shallow sulcus due to shrinkage of the area of the trigeminal nucleus and tract. *A*, fibers of the spinal trigeminal tract; *B*, afferent fibers of the dorsal root; *C*, longitudinal fibers of the medial zone of the trigeminal nucleus. (*b*) Photomicrograph of section taken at the level of the caudal end of the medulla oblongata. There is marked degeneration of the spinal trigeminal tract. A number of fine fibers are present in the dorsal part of the tract. Weigert stain for myelin; × 22.

Nucleus of the Spinal Tract of the Trigeminal Nerve.—This complex showed a distinct shrinkage in the lower levels; it was not more than a third of the size of that on the opposite side. Though on section the

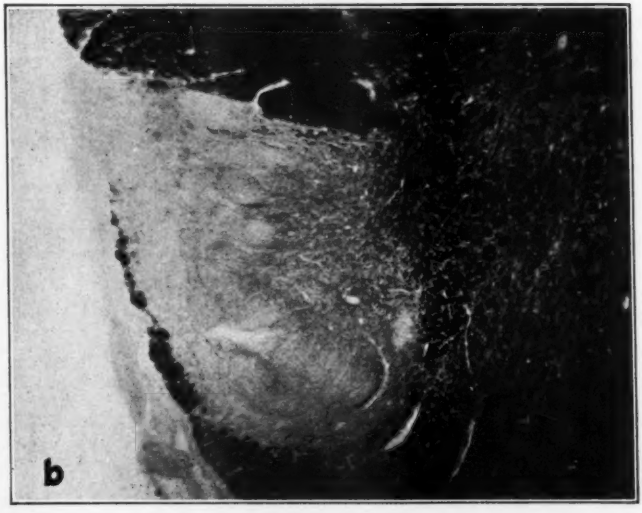

Fig. 3.—(*a*) Drawing to show the level of the section (*b*) which was taken at the upper end of the pyramidal decussation. Note the absence of a tuberculum cinereum on the left side. *A*, fibers of the spinal trigeminal tract; *C*, longitudinal fibers of the medial zone of the trigeminal nucleus; *D*, secondary trigeminal fibers; *E*, concomitant fibers of the trigeminal nucleus. (*b*) Photomicrograph of an intermediate section between the caudal end of the specimen and the site of the incision. The well marked dorsal spinocerebellar fibers partly cover the area of the degenerated spinal trigeminal tract. Weigert stain for myelin; × 22.

nuclei gelatinosi trigemini are frequently unequal in size, the difference in this specimen was too great to be considered normal. The characteristic fine fiber network in the medial part of the nucleus appeared less dense than normal; this may have been due to the lack of the normal number of spinal tract collaterals. There were also fewer longitudinal

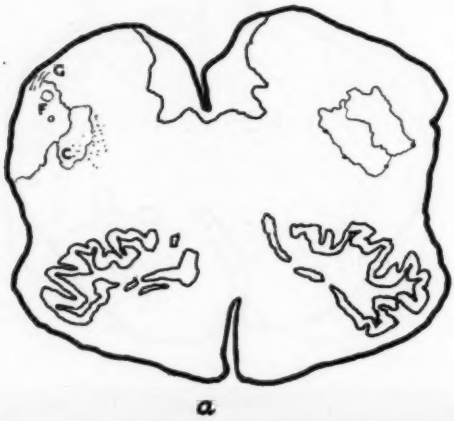

Fig. 4.—(*a*) Drawing to show the level of the section (*b*) which was taken at the point of operative incision. *C*, longitudinal fibers of the medial zone of the trigeminal nucleus; *F*, areas of cystic spaces; *G*, dorsal spinocerebellar fibers. (*b*) Photomicrograph of a section at a level just below the middle of the olive. There is interruption of the fibers of the spinal trigeminal tract. The incision has been passed through the dorsal spinocerebellar fibers and reaches the lateral part of the spinal trigeminal nucleus. Weigert stain for myelin; × 22.

fasciculi of the internal zone of the nucleus than on the opposite side. The thick bundles dorsomedial and medial to the nucleus were the afferent fibers of the dorsal root. These tended to obscure the secondary

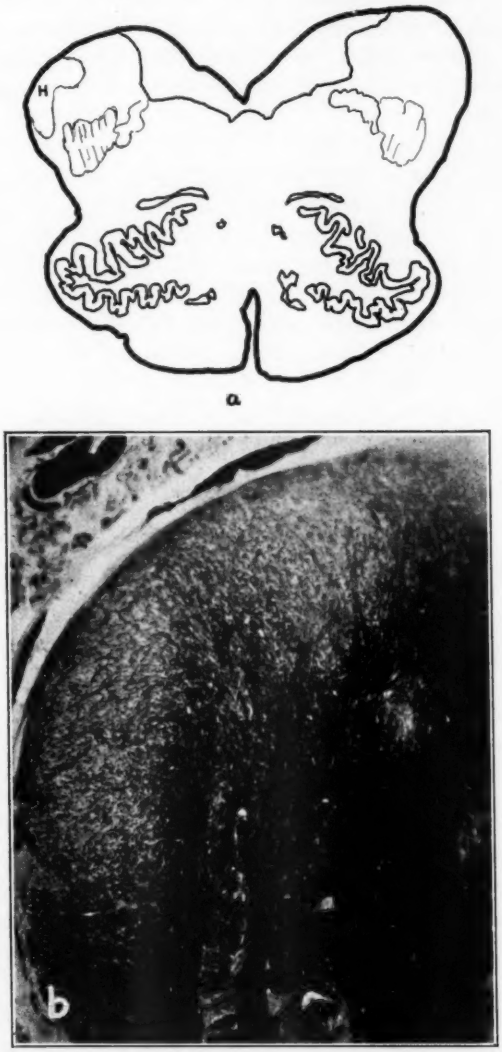

Fig. 5.—(*a*) Drawing of a section (which is slightly oblique) which was taken above the site of the incision. *H*, area of degeneration of spinocerebellar fibers. (*b*) Photomicrograph of section through the restiform body showing a reduction of its fibers. Weigert stain for myelin; × 14.

trigeminal fibers in this region, which occupied a small area medial to the nucleus. Sections 1 or 2 mm. higher showed the secondary trigeminal fibers leaving the nucleus. These were distinct at the level of the upper limit of the pyramidal decussation (fig. 3 *a* and *b*); at this level there were distinctly fewer longitudinal fasciculi in the internal zone of the trigeminal nucleus than on the opposite side. The concomitant fibers of the descending nuclear complex appeared to be about equal on the two sides.

Nucleus of the Spinal Tract at the Site of the Operative Incision: This appeared to have been encroached on by the tractotomy knife. There were fewer longitudinal fasciculi in the internal zone of the nucleus. The concomitant fibers just medial to the nucleus were about equal in number to those of the opposite side. The secondary trigeminal fibers leaving the nucleus at this point could not be definitely distinguished. If the trigeminothalamic (quintothalamic) tract was demonstrable by degeneration, it should have been seen at these levels, but it was not to be found.

Changes Above the Level of the Operative Incision.—In sections through the restiform body (fig. 5 *a*) the damage to the spinocerebellar fibers can be assessed. About 20 to 25 per cent of the fibers were damaged (fig. 5 *b*). In these sections the nuclei (proprius and marginalis) of the restiform body did not interfere with an estimate of the degeneration in the dorsal spinocerebellar fibers, which was distinct up to about the level of the entrance of the cochlear nerve. The trigeminal nuclei appeared normal, as did the concomitant fibers. A trigeminothalamic tract could not be distinguished. Presumably a few cerebellar fibers from the opposite inferior olivary nucleus were also cut, though no change could be seen in the nucleus.

Higher sections at the entrance of the superior cerebellar peduncle into the tegmentum showed no definite changes.

COMMENT

Though the patient did not get relief from his pain, it can be seen that the incision in the brain stem was well placed, the great majority of the fibers of the spinal tract of the trigeminal nerve having been severed. It is unlikely, though possible, that the few fibers which escaped section were responsible for conduction of painful impulses.

The shrinkage in the caudal part of the trigeminal nucleus, as previously described, may account for the continuance of the pain following the tractotomy. If, indeed, the pain did arise at this level, then it is obvious that even a complete tractotomy could not have relieved it.

The analgesia in all three divisions of the trigeminal nerve demonstrates that pain fibers in these divisions enter the trigeminal nucleus (nucleus gelatinosus) not higher than just below the midolive level. Also the postoperative sensory changes confirm the generally accepted view of the representation of pain, temperature and touch sense in the nuclear complex of the spinal tract of the trigeminal nerve.[2]

No trigeminothalamic tract (either dorsal or ventral) could be demonstrated. It would be difficult to show a minor degeneration affecting such a tract in material stained by Weigert's method. The Marchi technic was applied to a number of sections; though this method may be used successfully some months after damage to fibers, no result was obtained in this material. Since secondary trigeminal fibers could be seen leaving the nucleus, the lesion in the trigeminothalamic tract must have been small; probably the damage was confined to the site of the operative incision.

The patient had some disturbance of equilibrium which might be attributed to the interruption of the fibers of the restiform body. However, it could be due to disturbance of the cerebellum at operation, just as the nystagmus was probably due to manipulation affecting part of the vestibular system. In any case, in spite of the section of the spinocerebellar fibers, the patient became well compensated. This suggests that when the operative incision is not above the midolive level cases of lack of compensation for injury to components of the restiform body, such as that mentioned by Olivecrona,[3] may be due to some cause other than the operative interruption of cerebellar afferents.

The impairment of taste noticed by the patient is not usually mentioned as the result of tractotomy. This may be explained by differences in the site of the incision; in this case there was probably damage to the taste fibers of the tenth nerve, which at these levels pass dorsomedially in close relation to the spinal tract of the trigeminal nerve to the gustatory nucleus, in the floor of the fourth ventricle.

Since the specimen had been mordanted for Weigert's method, it was not possible to make satisfactory cytologic studies. In a specimen of this kind, with minimal postmortem changes, if the material was fixed and prepared for Nissl's staining the cytologic changes might be correlated with the findings in the fiber systems. By this means it might be possible to obtain information as to the function of the different types of cells in the nucleus of the spinal tract of the trigeminal nerve.

2. Ranson, S. W. R.: The Anatomy of the Nervous System, ed. 8, Philadelphia, W. B. Saunders Company, 1947.

3. Olivecrona, H.: Tractotomy for Relief of Trigiminal Neuralgia, Arch. Neurol. & Psychiat. **47**:544 (April) 1942.

SUMMARY

The changes in the spinal tract and nucleus of the trigeminal nerve nine months after a trigeminal tractotomy which failed to relieve the neuralgia have been studied in a specimen of medulla and pons. These changes consisted in degeneration of the descending tract below the level of the operative incision with shrinkage of the substantia gelatinosa trigemini in the lower levels of the medulla and with minor changes in associated fiber systems. A trigeminothalamic tract could not be demonstrated. A comparison of the clinical observations and the histologic evidence confirms the more generally accepted view as to the representation of pain, temperature and touch sense in the spinal tract of the trigeminal nerve.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ACETYLCHOLINE AND NEUROMUSCULAR TRANSMISSION. MARIANNE FILLENZ and MARY HANAFIN, J. Neurophysiol. **10**:189 (May) 1947.

Fillenz and Hanafin produced complete block of neuromuscular transmission by soaking the frog's sartorius muscle in a 1 : 500,000 solution of acetylcholine chloride in the presence of a 1 : 100,000 solution of neostigmine. Under these conditions a nerve impulse still sets up an end plate potential, which in ideal circumstances is slightly larger than the curare end plate potential and has a time course resembling that of the curare-neostigmine end plate potential.

The end plate potential set up by rapid repetitive stimulation exhibits on cessation of stimulation rather discrete fast and slowly decaying components. The slow component is small with the curare end plate potential and is selectively increased by neostigmine. It is also large with the acetylcholine end plate potential.

FORSTER, Philadelphia.

ACETYLCHOLINE AND SYNAPTIC TRANSMISSION IN THE SPINAL CORD. J. C. ECCLES, J. Neurophysiol. **10**: 197 (May) 1947.

Eccles abolished cholinesterase activity in the spinal cord of the frog by the use of neostigmine. The cord was then immersed in strong solutions of acetylcholine. He found that neostigmine has no detectable effect on the synaptic potentials set up in the anesthetized spinal cord by dorsal root volleys even when they are rapidly repetitive. Strong acetylcholine solutions have about the same depressant effect on the synaptic potential as on the end plate potential. The author concludes that acetylcholine does not mediate synaptic transmission in the frog's spinal cord.

FORSTER, Philadelphia.

CEREBRAL REGULATION OF MOTOR COORDINATION IN MONKEYS FOLLOWING MULTIPLE TRANSECTION OF THE SENSORI-MOTOR CORTEX. R. W. SPERRY, J. Neurophysiol. **10**:275 (July) 1947.

Sperry made multiple intersecting knife cuts in the sensorimotor cortex of monkeys. The incisions extended through the gray matter in a vertical plane so as to interrupt the horizontal intracortical transmission, leaving intact connections through the white matter. When the incisions extended only as deep as the upper third of the sixth layer, the effect on motor coordination was negligible. Symptoms of functional depression became increasingly apparent as the incisions extended into the white matter. With the electrostimulable foci of the various components of the arm area permanently separated by incisions no permanent motor impairment was noted, and electrical stimulation produced typical motor reactions after functional recovery had taken place. The symptoms noted were those of afunction and depression, and not of positive disorganization, and are correlated primarily with invasion of the white matter.

Sperry concludes that these experiments failed to confirm theories of cerebral function which have assumed that horizontal intracortical transmission either of discrete excitations or of mass field forces plays any major or essential role in cerebral organization.

FORSTER, Philadelphia.

Neuropathology

SUBDURAL HAEMORRHAGE, CYSTS AND FALSE MEMBRANES, ILLUSTRATING THE INFLUENCE OF INTRINSIC FACTORS IN DISEASE WHEN DEVELOPMENT OF THE BODY IS NORMAL. KEITH INGLIS, Brain **69**:157, 1946.

Inglis studied 9 cases of subdural hematoma, in 3 of which there were a delicate false membrane and small extravasations of blood in the false membrane and in 2 cases a considerable amount of blood on the deep surface of the dura. In these cases hemorrhage was the outstanding gross feature. In 1 case of subdural hematoma the hemorrhage appeared grossly to be intradural; in 1 case a subdural cyst, and in another a false subdural fibrous membrane were present. From the study of these cases and from correlations with similar reported instances of subdural bleeding, Inglis concludes that subdural hemorrhagic false membranes are due not to inflammation but to irritation by the blood of the cells lining the dura mater. These lining cells differ from lining cells of serous membranes, since the cells are modified connective tissue cells, and may even exercise phagocytic activity. The reaction of these cells to extravasated subdural blood is the same regardless of the cause or the size of the extravasation. Delicate membranes, cysts and fibrous membranes are of essentially the same nature. The distinctive feature of the reaction of these cells is that it results in the formation of a false membrane loosely attached to the dura and free of the arachnoid, which takes no part in its formation. The process is progressive and is not scar forming. Inglis suggests that the essential condition responsible for these distinctive features may be related to the neuroinsulation theory of Trotter and depends on the maintenance of the barrier between neural and non-neural tissues.

FORSTER, Philadelphia.

DEMENTIA WITH PALILALIA IN AN ADOLESCENT: CORTICAL AND SUBCORTICAL LESIONS DUE TO DIFFUSE CEREBRAL ENDARTERITIS. L. FROMENTY, Encephale. **38**:49, 1949.

Fromenty reports the case of a white girl aged 20 with no familial, hereditary or personal disease of any significance. Until the age of 15 she had been considered healthy, robust and normal. Her disease began insidiously with an increasingly poor scholastic effort, followed within two years by dementia. She remained at home, lazy, inert, dreamy and indifferent with occasional long fugues, during which she wandered about. On examination in 1943, she showed puerile, agitated behavior, was slovenly in dress and comportment, had pronounced disturbances of association and thinking (bleulerian type) and was inattentive with intermittent palilalia. In the hospital she exhibited mental confusion and was violently agitated, refusing all food. Moderate spiking fever was attributed to pulmonary tuberculosis of the right lung, which cleared before her death. The course during her last three months of life was marked by increasing cachexia, stupor, mutism, delirious episodes and, always, a prominent palilalia. She died about eighteen months after she was first studied, of perforation of the intestine. The author especially notes that the palilalia was intense and that it paralleled her mental confusion and agitation.

She also exhibited logorrhea, with no formed phrases or sentences; there was no word salad. The logorrhea seemed explosive and compulsive. Neurologic examination was essentially noncontributory.

The entire brain was sent to Prof. O. Vogt's laboratory, in Neustadt, Germany, where it was sectioned and studied. It weighed 1,130 Gm. There were two types of lesions, the vascular and the parenchymatous. The vascular lesions were of peculiar type and diffuse, with extensive changes in arteries and arterioles of the gray matter of the cortex and the central nuclei. There was conspicuous hyperplasia of the vascular endothelium with many occluded vessels. There was some formation of new vessels. The lesion was an endarteritis with a tendency to obliteration, but nowhere was there any inflammatory lesion, cellular infiltration, either in the wall or in the perivascular spaces, thrombi, emboli or softening.

Lesions of the second type involved the nerve tissue itself. The cortical cells showed regression, with disappearance of cells in some areas. The tigroid material had disappeared; the cells were contracted and showed fatty vacuolation. The nuclei of the cells showed hyperchromatosis, progressing to pyknosis. The cellular lesions were not similar to those observed in schizophrenia. The disappearance of nerve cells was prominent in the left third frontal gyrus (Broca's area), as well as in the insula. Other frontal and perfrontal gyri were intact. There were less prominent lesions in the temporal lobe; these were localized to the third cortical layer (second sublayer of the third layer of cortex), involving the layer of medium-sized pyramidal cells. There was no evidence of neuroglial reaction. The striate body showed vacuolar degeneration with the cell nuclei in fair state. The lesions were more pronounced in the putamen than in the caudate nucleus; but the maximal disturbance was in the globus pallidus, where it was greater than in the cortex itself. There was conspicuous disappearance of cells without neuroglial reaction. Tuberculosis was considred as the cause of death.

The course of the disease clinically suggested schizophrenia, but at no time in the five years had there been any catatonic or paranoid features. The histologic study of the lesions were not those of dementia precox. Buerger's disease (thromboangiitis obliterans), cerebral type, was considered but was ruled out by the pathologic picture. The origin remains a mystery. The author makes a plea for more complete and systematic anatomoclinical studies in psychiatric cases.

ZINKIN, New York.

Psychiatry and Psychopathology

PSYCHOTIC REACTIONS TO INGESTION OF LARGE DOSES OF QUINACRINE [ATABRINE®] IN NORMAL SUBJECTS. S. W. HOOBLER, Am. J. Trop. Med. **27**:477 (July) 1947.

According to Hoobler, cases of psychic disturbances following the treatment of malaria with quinacrine [atabrine®] have been reported by a number of authors. In such instances it has usually been impossible to exclude the malaria itself or some hypothetic toxic substance resulting from the rapid destruction of a large number of parasites by quinacrine as the cause of the mental disturbance. It was decided therefore to investigate the effect of this agent on nonmalarial subjects. In 24 of 31 officers who were taking for the first time moderate doses of quinacrine in excess of those used in routine antimalarial therapy there developed toxic symptoms referable to the central nervous system, varying from mild insomnia and depression to severe psychotic reactions, the latter occurring in 3 subjects. Since

malaria was definitely excluded in every instance and the reaction subsided promptly on discontinuation of the drug, quinacrine alone could be definitely implicated as the cause of the psychic reactions encountered.

J. A. M. A.

TRENDS OF VOCATIONAL ACHIEVEMENT IN MENTAL DISORDER. A. I. RABIN, Scient. Monthly **65**:213 (Sept.) 1947.

In a study of 1,000 patients in state hospitals and an equal number from the general population, Rabin offers interesting figures concerning the occupational categories of psychotic and nonpsychotic persons. His categories are: (1) professional, (2) clerical, (3) service, (4) farming, (5) skilled and (6) semiunskilled. The percentage of patients reaching professional status was only one-half the normal expectancy. In the clerical group the percentage of the patients was somewhat higher than the normal, whereas in the service group it was almost twice as great. In the other groups practically no difference was observed.

The psychoses are reported as (1) psychoneurosis, (2) manic-depressive psychosis and (3) schizophrenia. The professional category had a high percentage of psychoneurotic patients and a low percentage of schizophrenic patients, with the patients with manic-depressive psychosis in between. The patients with manic-depressive psychosis were predominant in the clerical and service groups, while the semiunskilled group showed the highest percentage of schizophrenic patients. In the other groups the percentages for the psychoses were very nearly equal. The skilled group, however, showed the smallest number of schizophrenic patients of all groups.

Rabin considers that schizophrenia is chiefly responsible for the low occupational level of the entire patient group. "In schizophrenia the onset of the disorder is gradual even prior to its overt manifestations, thus preventing early occupational adjustment commensurate with the individual's capacities and educational background and opportunities."

CASAMAJOR, New York.

Diseases of the Brain

UNILATERAL SYPHILITIC PRIMARY ATROPHY OF THE OPTIC NERVES. WALTER L. BRUETSCH, Arch. Ophth. **39**:80 (Jan.) 1948.

Bruetsch reports an anatomic study of 2 cases of unilateral syphilitic optic nerve atrophy in which death occurred at a time when the atrophy was confined to only one optic nerve. One patient had dementia paralytica and the other meningovascular syphilis. With regard to the first case, Bruetsch states: "The anatomic evidence, which could be pieced together from serial sections, pointed to the intracranial portion of the optic nerves as the starting point of the disease process. The syphilitic exudate in the interior of the nerves had reached its greatest intensity in the demyelinated portion of the left, atrophied, optic nerve. However, a similar, but less intense, inflammatory process was already present in the intracranial portion of the not yet demyelinated right optic nerve. One can safely assume that the exudative process in the already demyelinated left optic nerve has preceded, possibly by several years, the appearance of the syphilitic exudate in the interior of the other, not yet atrophied, nerve. Demyelination of nerve fibers in primary syphilitic optic nerve atrophy is, as a rule, an exceedingly slow process, being the result of a mild, but persistent, inflammation."

He comments on the second case thus: "In this patient with meningovascular syphilis and unilateral atrophy of the optic nerve, the syphilitic meningitis was almost exclusively confined to the base of the brain. The meningitic exudate had reached its height over the left side of the anterior portion of the chiasm, where

the left optic nerve emerges, having produced complete demyelination in this area. Since in most cases unilateral atrophy of the optic nerve becomes bilateral, it was of great interest to ascertain the degree of the inflammatory reaction in the nondemyelinated part of the chiasm and in the right, nonatrophied, optic nerve. In the not yet demyelinated portion of the chiasm and in the still normal optic nerve there was already at this stage enough syphilitic exudate to have led to demyelination of the nerve fibers in the near future. A great deal has been written on the direct noxious action of spirochetes on the nerve fibers in optic nerve atrophy. For this reason, a most intensive search for spirochetes was made in the optic pathways and in other regions of the brain, but none were found."

It is apparent, therefore, that unilateral primary syphilitic atrophy of the optic nerve is almost always the forerunner of bilateral atrophy, and it is likely that syphilitic optochiasmatic arachnoiditis, which is frequently present in neurosyphilis, has nothing to do with the atrophy of the optic nerves.

SPAETH, Phladelphia.

Diseases of the Spinal Cord

INVOLVEMENT OF EYES IN POLIOMYELITIS. R. COLLIN and W. L. BASSENEGE, Klin. Monatsbl. f. Augenh. **113**:255, 1948.

Collin and Bassenge made ophthalmologic studies on 40 patients who had received treatment in the "iron lung" in the course of the epidemic of poliomyelitis in Berlin in 1947, in which a total of 2,300 cases were reported. Seventy other patients with poliomyelitis who did not require treatment in the "iron lung" were also given a thorough examination of the eyes. The ophthalmologic examination was repeated at regular intervals, so that it was often possible to observe the appearance and rapid disappearance of symptoms. A third group, of 40 patients, who had persistent spinal paralysis after an attack of poliomyelitis were examined for late ocular symptoms. Three and one-half months was the time that had elapsed after the acute attack. Involvement of the eyes is not rare in poliomyelitis. Nuclear and supranuclear paralysis of the facial nerve, ptosis, abducens paralysis and paralysis of the internal rectus muscle were observed. There is a good prospect that these types of paralysis will subside. In the cases of poliomyelitis in which lesions exist in the upper part of the spinal cord, involvement of the sympathetic fibers may produce disturbances in the pupils. The majority of the patients who required treatment in the iron lung showed signs of stasis in the retinal vessels and in the optic papilla. Although optic neuritis was not encountered during this epidemic, it may be expected to occur. The authors believe that in patients with obscure paralysis of some of the cerebral nerves the cases of poliomyelitis should be considered. It is advisable to hospitalize these patients, not only for prevention of further spread of the poliomyelitis but also for the special care which may become necessary, since the lesion is close to the respiratory center.

J. A. M. A.

Peripheral and Cranial Nerves

MICROSCOPIC STUDY OF THE INNER EAR OF THE ATAXIC RABBIT. M. V. ANDERS, Arch. Otolaryng. **46**:335 (Sept.) 1947.

Hereditary loss of coordination occurring in a race of domestic rabbits was recently reported, the neuropathogenesis of this disorder proving to be an initial degeneration of the vestibular and cochlear nuclei, with resulting breakdown of

the central pathways of these systems. Histologic studies on the inner ears of 10 ataxic rabbits and 5 entirely unrelated, normal controls showed no structural changes in the sensory end organs of the cochlea and vestibule.

RYAN, Philadelphia.

UNUSUAL CAUSE OF IRRITATIVE MEDIAN NEURITIS IN THE HAND. P. D. BEDFORD, Lance **1**:597 (May 3) 1947.

Bedford reports the case of a man aged 30 in which pain developed in the distribution of the ulnar communicating branch to the median nerve, deep pressure near the hook of the hamate bone causing severe pain along the digital branches of the median nerve. The history revealed that the patient played squash frequently and had been using a new racquet with the handle causing pressure near the hook of the hamate bone. Symptomatic treatment relieved the pain. The patient has been using a different type of racquet and has had no recurrence.

MADOW, Philadelphia.

PAINFUL SEQUELAE OF INJURIES TO PERIPHERAL NERVES. S. SUNDERLAND and M. KELLY, Australian & New Zealand J. Surg. **18**:75 (Oct.) 1948.

In the 278 cases analyzed by Sunderland and Kelly, severe pain in the hand or foot persisted for at least five weeks after the receipt of an injury to a nerve trunk and the pain was not related to damage or to involvement of non-neural tissues. The term causalgia has been applied to this pain, which is primarily a sequel of gunshot lesions in which stretch of the nerve appears to play an important part. In the great majority of cases it follows damage to the main sensory pathways from the palm or the sole. The higher in this pathway the level of the lesion, the more likely is causalgia to ensue. Its incidence bears no relation either to neuroma formation or to the degree of visible damage to nerves or other tissues. Though sympathectomy has proved valuable, there is no other evidence to suggest that the sympathetic system is especially involved. The clinical evidence suggests that the painful sequelae of nerve injuries are the effect of the spread of damage to the central nervous system by retrograde and transneuronal changes. A center of abnormal spontaneous activity is thereby set up in the cord, which acts as a focal point for the dissemination of spreading disturbances, involving wider and wider areas of the cord. These produce effects on the peripheral tissues via adjacent posterior roots (hyperalgesia), while a succession of abnormal impulses reach the cerebrum, producing effects on the sensorium (spontaneous pain). Anatomic and physiologic evidence is produced which lends support to this interpretation. In most cases of causalgia there is spontaneous cure, and surgical treatment should therefore be reserved for the cases of severe and stubborn causalgia.

J. A. M. A.

Treatment, Neurosurgery

PENICILLIN THERAPY ALONE IN NEUROSYPHILIS: AN ANALYSIS OF CLINICAL RESULTS. GEORGE D. GAMMON, JOHN H. STOKES and others, Ann. Int. Med. **25**:412 (Sept.) 1946.

The observations reported in this study were made on patients with neurosyphilis. All patients were treated with penicillin alone. Observations were first

made in November 1943, and the last observations were made about two years later. The diagnostic categories and the period of follow-up observation are as follows:

Diagnostic Category	No. of Cases	Follow-Up Period, Months			
		24 to 18	18 to 12	12 to 6	6 to 4
Dementia paralytica	19	5	3	7	4
Tabetic form of dementia paralytica	28	6	2	11	9
Juvenile dementia paralytica	10	1	2	3	4
Tabes	54	8	17	19	10
Meningovascular neurosyphilis	31	9	8	9	5
Asymptomatic neurosyphilis	19	4	2	8	5
Total	161	33	34	57	37

From the data obtained, the results, as measured clinically and by changes in the blood and spinal fluid, indicated that penicillin is an active therapeutic agent. The authors summarize their findings as follows:

The greatest effect was observed in the mental breaks, the incoordination and the tremors and speech defects of dementia paralytica and in the lightning pains of tabes. Fixed pupils, absence of reflexes and other signs of destructive lesions did not improve. Abnormalities of the spinal fluid were particularly responsive to penicillin. The effect on patients with asymptomatic neurosyphilis was greatest and on patients with dementia paralytica least. Responses of the blood are less than responses of the spinal fluid.

Penicillin is the first choice for the first treatment of neurosyphilis. This statement may be qualified in cases of dementia paralytica. In these cases failure to improve promptly indicates further treatment, either more penicillin or induced fever. Dosage schedules are discussed in the light of the various factors involved, including the changing character of penicillin. Adequate clinical and spinal fluid follow-up observation is essential.

Several important factors must be emphasized. When these studies were first undertaken, penicillin was given intramuscularly every four hours. Later, the drug was administered routinely every three hours for a period of eight days, until the dose totaled 1,200,000 to 2,400,000 Oxford units. Since May 1945 a new dosage system, in which the total dose is 4,800,000 units, has been employed. This is given in three ways: as a single course within eight days, as a single course within sixteen days and as two courses of 2,400,000 units each within eight days, the courses being administered seven months apart. In addition to this standard therapy program, a dose of over 4,800,000 units was given in exceptional cases. A few patients received three courses.

The results which have been presented in this paper must be interpreted in the light of the fact that from June 1943, the date of inception of the study, to the present time, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as the potency, in terms of units per milligram, has increased. The relative amounts of the several identified penicillin fractions, G, F, X and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant, and that it may be significantly different today from what it was originally. It is now impossible to assess the extent to which these changes may have affected the results here reported.

GUTTMAN, Wilkes-Barre, Pa.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Kenneth J. Tillotson, M.D., *Presiding*

Regular Meeting, Dec. 5, 1946

Applications and Limitations of Electroencephalography in a General Hospital. DR. ROBERT S. SCHWAB.

At the Massachusetts General Hospital since 1938, the electroencephalographic laboratory has received patients for the test by ordinary requisition of members of the staff in the same way as for roentgenologic, electrocardiographic and other laboratory tests. This communication is a report of a spot check of 100 consecutive electroencephalograms made in August 1946, which were carefully correlated two months later with the final clinical diagnosis and a perusal of the hospital record. The survey shows clearly that the electroencephalogram, as it functions in a general hospital, has taken on some of the unpleasant burdens of other diagnostic laboratories, namely, that of reassurance of both physician and patient that no physical disease exists and of rounding out the complete work-up of a diagnostic study.

Workers in the field of electrocephalography do not like to spend a long hour in a sixteen lead study of a neurotic or demanding patient simply because his physician, in his hurry, has ordered the best of every diagnostic test, instead of fitting it into the actual clinical work-up of the case by consultation with the laboratory. On the other hand, one never knows when a simple headache may show, during a careful study of localization, an electric focus which may be the earliest sign of the tumor. Nor can one set up complicated and irritating barriers to hinder the busy visiting or house physician of a large hospital so that he will omit the test altogether. The electroencephalographer must accept the burden of making useless tests in order to keep a steady flow of interesting and worth while diagnostic problems in which the electroencephalogram may be of aid.

In the present series of 100 cases, the records of 54 were reported as normal, and 50 of these reports were in clinical agreement with the diagnosis of no organic disease of the brain when the patient left the hospital. In 46 cases the records were abnormal, and in 36 of these the reports were in clinical agreement with the presence of an organic disease of the brain. The records in 24 of these 36 cases confirmed the clinical diagnosis of epilepsy; in 12 cases the tracings showed abnormal focal waves agreeing with the diagnosis of an intracranial lesion, such as a tumor, scar, subdural hemorrhage or abscess. In 5 cases, the electroencephalograms, although abnormal and in agreement with the general clinical impression that the brain was abnormal, failed to localize the abnormality correctly. In 4 cases the abnormal electroencephalogram was the most important clue to the correct localization of the lesion. In 4 cases it was the significant positive evidence in the diagnosis of epilepsy. In 36 of the 46 cases in which the electroencephalograms were abnormal, the report simply confirmed the clinical diagnosis, and the test might well have been omitted had diagnostic economy been essential. In 6 cases the electroencephalographic report was of no value and, if given weight, would have been misleading, and in 6 cases it contributed nothing of value in either direction.

In summary, then, in a general hospital the electroencephalogram was of clinical value in about 82 per cent of cases, confirming the clinical diagnosis of absence of the cerebral disease or of its presence, and possibly its location; in 8 per cent it was a critical factor in leading to the correct diagnosis; in 12 per cent it was of no value whatever, and in 6 per cent it might have contributed to an erroneous diagnosis.

DISCUSSION

DR. W. GREY WALTER, Bristol, England: It might encourage Dr. Schwab to learn that my colleagues and I have made an analysis of 10,000 cases in Bristol in the last six or eight years, including a number of war casualties, and our figures could almost be superimposed on his, obtained with different methods and different criteria and based on different types of cases.

Brain Wave Frequencies and Brain Chemistry. DR. HUDSON HOAGLAND, PH.D., SC.D.

My colleagues and I have found that the energy of activation as calculated by the Arrhenius equation, which relates chemical velocities to temperature, is useful in delineating the slowest step in a sequence of enzyme-catalyzed reactions. Such slow steps constitute chemical pacemakers for the over-all sequence of reactions involved in cellular respiration.

Most nerve centers of both vertebrates and invertebrates show rhythmic fluctuations in voltage at frequencies ranging roughly from 1 to 30 cycles per second. These chemically determined frequencies are modified by afferent discharges, but they occur in the absence of such modification. The regular, sinusoidal, alpha brain waves, with a frequency of about 10 per second, recorded from large areas of the human cerebral cortex furnish an example of the phenomena. Evidence indicates that brain cells produce potential gradients as a by-product of their respiratory metabolism. These may be of the nature of diffusion potentials across the cell membranes, which possess definite electrical impedance and which discharge when the potentials reach a critical value. In such a system the discharge frequency depends on the speed with which the metabolic factor can load the capacities of the cell walls to their critical firing potentials. The absolute frequency is thus determined by the rate of cellular respiration and by the electrical impedance of the cell walls. If this impedance is statistically constant for a particular group of cells under the conditions of the experiments, the frequency should parallel and be a measure of changes in cortical respiration. To test this hypothesis, metabolic stimulants, such as dinitrophenol and thyroxin, were shown to increase the frequencies of alpha waves. A marked lowering of the blood sugar, so that the brain is deprived of its principal fuel, or a considerable decrease in the oxygen consumption of the brain slows alpha frequencies. Most significant of all, however, have been studies of the effect of temperature on the frequencies of brain waves and corresponding in vitro studies of the effect of temperature on the kinetics of simple enzyme systems known to be functional in cerebral respiration. This work has furnished information as to how one or the other of the links in the chemical chain constituting cortical respiration may act as chemical pacemaker, or master reaction, to control the alpha frequency. Under certain conditions, for example, it has been shown that the dehydrogenation of succinate may be the pacemaker step; in other conditions the role evidently belongs to the cytochrome oxygen–activating link. This work has been applied specifically to the analysis of chemical pacemaker changes in advancing syphilis of the brain (dementia paralytica).

We have demonstrated that with the advancement of spirochetal infection of the brain in dementia paralytica, first one, and later another, enzyme-catalyzed link in the oxidation of carbohydrate by the cerebral cortex becomes the limiting factor (bottle neck), or chemical pacemaker, for cortical respiration. Accompanying these pacemaker shifts are advancing degrees of psychotic behavior. For example, our evidence both from in vivo and from in vitro studies indicates that the step involving the cytochrome system in cortical respiration is the slowest one, and hence the limiting chemical pacemaker in advanced dementia paralytica. In intermediate states of the disease the succinodehydrogenase step appears to be the limiting factor, whereas in normal persons and in patients with early dementia paralytica a third, as yet unidentified, enzyme system is the chemical pacemaker. As yet we have been unable to test this view with other types of psychotic patients, although Freeman's report of a low iron content of the brain of schizophrenic patients is at least consistent with the hypothesis that the iron-containing cytochrome system may be the limiting factor in the cerebral respiration in this group.

In our studies of chemical pacemakers we showed by several procedures that changes in the frequencies of dominant cortical alpha rhythms were proportional to changes in cortical respiration. In our series of experiments on chemical pacemakers we found further that when temperature (by means of diathermy) accelerates these rhythms, their energies of activation, calculated by the Arrhenius equation, were identical with those obtained by studies of oxygen consumption in Warburg manometers for extracted specific respiratory enzymes when these enzymes are the limiting factors for oxygen consumption. A review of the foregoing material and citations is given by H. Hoagland (Chemical Pacemakers and Physiological Rhythms, in Alexander, Jerome, Colloid Chemistry, Theoretical and Applied, New York, Reinhold Publishing Corporation, 1944, vol. 5, pp. 762-785).

A variety of evidence exists implicating derangements of brain metabolism in psychotic patients. These derangements would not necessarily be expected to be reflected in the oxygen consumption of brain as measured by differences in oxygen content of arterial blood and of venous blood coming from the brain. The brain operates on a considerable factor of safety for both its oxygen and its glucose supply. The limiting factor in tissue respiration is seldom the initial substrate concentrations, but, rather, is the extent to which the enzymes involved are capable of saturation with their respective substrates. Thus, the over-all oxygen consumption of the psychotic brain might be normal, but some one or more of the series of intermediate enzyme-catalyzed steps in the oxidation of glucose might be so altered as to produce effects that would modify cellular excitability and tissue function.

DISCUSSION

DR. LESLIE F. NIMS, New Haven, Conn.: Dr. Hoagland is to be congratulated on the success he has achieved in the correlation of cerebral metabolism and certain features of the electroencephalogram. The chemical activity of the brain is difficult to study while it is functioning normally. In taking a biopsy sample for chemical investigation, one destroys the function. For that reason, one has but little information on the energetic governing electrical activity. Warburg experiments indicate possibilities and give clues to the source of chemical energy, but do not give answers. When it is remembered that electrical activity is but a manifestation of a physicochemical process, it is evident that Dr. Hoagland's methods are among the few possible means by which answers can be obtained.

A slide showing relations of the frequencies seen in the electroencephalogram to the level of carbon dioxide was shown. A real problem centers around the action of carbon dioxide in the central nervous system. Carbon dioxide, as well as other compounds, may exert its action by altering the acidity of the internal and external environments of the cells. This change in acidity would effectively modify the speed of chemical reaction by virtue of the known sensitivities of enzymes to altered acidity, and would thus change the frequency of electrical activity.

At one time carbon dioxide was called the "universal hormone" and was considered an important variable in regulating many of the tissue functions. It is generally believed that carbon dioxide regulates to a large degree the activities of the respiratory center. However, there is considerable resistance to the idea that carbon dioxide has an equally important role in the affairs of the brain. The respiratory center is but one extensive region of the central nervous system, and its properties must be shared to a variable degree by all regions of the central nervous system. The difficult task ahead is to find out exactly how carbon dioxide achieves its effects. It looks as though, to speak in very loose terms, the carbon dioxide directly controls the rate of oxygen consumption. The central nervous system has no reserve stores of oxygen and apparently cannot derive energy for electrical activity from anaerobic sources. Oxygen is necessary, but the level of carbon dioxide apparently controls, probably by many mechanisms, the utilization of available oxygen in the central nervous system. That carbon dioxide plays an important role is easy to demonstrate. One has only to hyperventilate for a few minutes and then introspect or examine the electroencephalograph. It is obvious that profound changes are going on in the central nervous system. What is the action of carbon dioxide in its intimate detail? What is its relation to the oxygen metabolism supplying the energy for the electrical activity?

Clinical Application of Automatic Analysis of the Electroencephalogram. Dr. W. Grey Walter, Bristol, England.

Interpretation of the electroencephalogram is limited not only by ignorance of brain physiology but also by the inadequacy of the unaided eye in resolving the components of a complex and irregular curve. Experimentally, it is difficult even for a highly skilled and experienced operator to detect more than the three major components of an electroencephalographic record—and there may be dozens. In order to overcome this basic hindrance to further advance, several types of analysis have been developed from time to time; the one to be demonstrated at this meeting has evolved through several more primitive forms and, though rather sleeker and more elaborate than is really necessary, it does at least supplement fairly adequately the limited capacity of the human eye, and, being automatic, relieves the recorder of some distraction.

The operating principle of the device is similar to that embodied in the ear—a set of tuned resonators, each connected to integrating and storage devices in such a way that the complex electrical oscillations (of which the primary electroencephalogram is a graph) are broken down into twenty-four components, with frequencies from 1.5 to 30 cycles per second, and the amount of activity at these various frequencies during a standard epoch of ten seconds is automatically written out over the primary tracing in red ink, in the form of a band spectrum, or frequency histogram. This is done every ten seconds, so that over 100 such analyses are performed during the ordinary routine electroencephalographic recording. In my laboratory in Bristol, the prototype of this instrument has made close on a million analyses in the course of the last few years, so at least my

colleagues and I have a fair idea of what it can and cannot do. Its advantages and achievements can be listed as follows: 1. It does not distract the operator's attention from the patient or the primary tracing. 2. The analysis is available soon enough to be of value in interpreting the record while it is being taken. 3. It permits resolution and location of components with an effective amplitude down to about 0.01 microvolt—several hundred times as small as can be seen on the primary tracing. 4. It can be checked and calibrated without external accessories. The most useful and dramatic application is that brain rhythms which are quite invisible in the primary electroencephalogram are not only identified but measured and located, though masked by other, larger, components. This can be done by connecting the analyzer between two channels of a bipolar chain; used in this way, the analyzer's true function, to assist in spatial analysis, is brought out clearly. Further elaborations are introduced by use of the averaging device, which permits an assessment of variance and stability of the various components over time periods from ten seconds to two minutes.

Among the limitations of the device may be noted the following: 1. In general, it cannot replace, but can only supplement, the ordinary primary electroencephalogram. 2. It cannot discriminate absolutely between artefacts and potentials of cerebral origin. 3. As with all types of analysis, mathematical or automatic, in certain circumstances the spectrum may be ambiguous in the sense that certain components may be "imaginary." An example is the "side band" phenomenon, seen when a rhythm of constant frequency varies in amplitude. Precise location of suspicious components will usually resolve the ambiguity in such cases. 4. Errors in tuning and adjustment are harder to detect than errors in the ordinary electroencephalograph and, if present, may lead to serious mistakes.

In the course of development, research and routine clinical use, the device has been applied to most of the subjects interesting to electroencephalographers, with results, of course, too numerous and varied to be summarized here. In the study of epilepsy, material has been collected which suggests that even in the period between seizures many of the electroencephalographic components recognized as a part of the seizure pattern are continuously present, and the hypothesis has been suggested that in some cases, at any rate, an epileptic seizure is associated with, and perhaps even the result of, exact synchronization of rhythms previously slightly out of step. In cases of acquired lesions, one of the first observations was that whenever a lesion involved the structures deep to the cortex rhythmic activity of 4 to 7 cycles per second was present, irrespective of the presence of cortical involvement. The hypothesis is offered that cortical lesions, whether slight or serious, are associated with slow, delta activity (1 to 3 cycles per second), whereas interference with corticobasal circuits introduces the 4 to 7 cycles per second component, which has been dubbed the theta rhythm because of the close association with lesions of the thalamus and around the third ventricle. Analysis is particularly important in cases of such lesions because the theta component is often small and masked either by the slow (delta) activity, in which it can be seen only as a distortion of the wave form, or by the normal (alpha) waves, with which it forms irregular beats and thereby loses its identity in the primary record. Tracing of the theta components is often of great value in appraising the extent and origin of a space-occupying lesion or the effects of trauma. Reports based on analysis of records can safely include much more detail than is usual in electroencephalographic practice, particularly when the responsiveness of the minor components to physiologic stimulation is included, for this part of the study often reveals which tracts and areas are still open and which are under attack by the disease process; ordinary electroencephalography usually distinguishes only

regions already overwhelmed. It has been found that the largest components in an electroencephalogram are by no means always the most significant; yet it is only these which are noticed without analysis of some sort.

Experience so far suggests that analysis of this type may serve two functions: 1. It can, when the complexity of interpretation required is no greater than that common at present, considerably accelerate the recording and consolidate the interpretation; in other words, it can make a good routine job easier. 2. It can, when desired, extend the scope and interest of electroencephalography to a point at which the experimenter sometimes feels that he may be starting to study brain physiology.

Charles L. Kubik, M.D., *Presiding*

Regular Meeting, March 28, 1947

Social Dissatisfaction and Personality Disorder. DR. JOHN C. WHITEHORN.

In the present stage of medical education, teaching is organized largely around functional concepts. In this context, psychiatry makes its principal contribution to general medicine through its psychodynamic insight into personality functions, gained through a better understanding of the emotional and unconscious aspects of personality. Through improvements in the methods of individual case study, psychiatrists have gained a vantage point from which they can understand in large part the clinical pictures of neurotic and psychotic patients as patterns of adaptive (or maladaptive) reaction, emotionally motivated. Although imperfect in many ways, psychiatry, so oriented, is useful to medicine in general. It gives helpful insight into human nature, especially those aspects of human nature particularly concerned with illness.

One source of imperfections in the psychiatrist's comprehension of human nature has been the tendency to consider the human being in a wholly individualistic light. He is awakening more definitely to the implications of the fact that man is inherently a social animal. In the attempt to clarify and emphasize this point, a formula for success and satisfaction has been expressed in the following words: "Satisfaction, in human living, is gained through successful spontaneous activity in a manner which maintains emotional security and self-assurance through the affection and respect of others."

Recent military experiences have provided overwhelmingly convincing evidence of the close relation between group morale and susceptibility to psychiatric disorder. Good group morale prevents neuroses; bad group morale breeds neuroses. Military morale is primarily a matter of emotional group solidarity and leadership, rather than of catchwords, slogans or neat rationalizations of why one has to fight. In the ultimate payoff, when the infantry has to take and hold the ground, the qualities of good leadership significant for high group morale—and for the prevention of psychiatric casualties—are, essentially, devotion to one's task and to one's men and a respectful sharing of knowledge as to objectives and means, implemented, of course, by a reasonable degree of mastery of technic and material. The parade ground virtues of leadership—the histrionic qualities associated with dictatorial leadership—are of relatively less importance in combat.

The personal emotional value of military group morale exemplifies in its clearest essence the fundamental feature of "social satisfaction"— the conviction of a shared purpose, together with the rewarding sense of value to one another in that purpose. In this experience, all are truly members, one of another. The more desperate the situation, the more immediately justified is one's conviction of

one's value to others, and therefore one's inherent worth. If the steadying light of a shared purpose is dimmed by mutual distrust, there is a break in the conviction that each can depend on the other to the limit of ability; the group morale may crack, and then the individual members crack and there is another crop of neuropsychiatric casualties.

Group morale determines group morals. What is good for the outfit is right. What is bad for the outfit is wrong. Psychiatrists have tended to avoid moralistic considerations as unscientific. The linkage of morals with morale and with susceptibility to neurosis establishes, however, the necessity of granting scientific psychiatric attention to moral issues in the broadened framework of the human being as inherently a social animal.

For purposes of such study, peacetime situations do not provide such clearcut pictures of unit morale and social satisfaction as does war. American "common sense" tends to ridicule "team spirit" and "enthusiasm" as "adolescent," while paradoxically exaggerating the value of the adolescent "virtue" of individualistic competitiveness and rivalry.

It is not easy to find or to develop opportunities for actual studies of the supportive and constructive values of social morale and social satisfaction in relation to personality disorder. It seems appropriate, therefore, to mention some of the studies in which I have taken a personal interest, as methodologic attempts:

1. Clinical case studies, which can yield much when made with care and imagination.

2. Social experimentation and observation on patients. At the Phipps Clinic, for about a year and a half, we have carried on a study of social interaction, almost like the study of gas molecules *in vacuo*, by setting up a unit for autistic children, who are characterized by a remarkable lack of social interest. In St. Louis, with Alfred H. Buchmueller, we studied the interpersonal contacts and relationships of patients in a small recreation room, observing the spontaneous formation and disruption of cliques, as a technic of personality study. In the armed forces there was a widespread development of diversified technic of "group psychotherapy." Many who participated therein or were stimulated thereby are experimenting along such lines now. Out of such studies should come a better appreciation of social forces in their relation to recovery of personal stability.

3. Studies on organized groups of presumably normal personalities, as in industrial plants and in schools. Alexander Leighton has utilized admirably the wartime Japanese relocation projects for the study of social sentiments and their operation in individuals and in groups, with special regard to clinical psychiatric considerations. He reported illuminatingly on the formation and functioning of political groups and the role of committees and boards in dealing with social dissatisfaction. Leighton noted the exaggeration of paranoid trends in leaders subjected to certain social pressures, as Kiene and Rosen also noted the efflorescence of paranoid reactions in certain Army officers when in command roles.

These studies are fragments in the development of a better-rounded psychiatry, in which the fruitful methods of individualized case study will be brought into better perspective with our increasing insight into the social nature of man.

DISCUSSION

DR. ABRAHAM MYERSON: I am glad to have been here and to have heard Dr. Whitehorn's evocative paper.

For many years it has seemed to me that at least one criterion of normality is somewhat askew. It is assumed that a person must adjust to society, that normality is manifested by adjustment and that adjustment proves normality.

But this implies a normal society; yet, in reality, one must adjust to a strong abnormal society. Therefore, social adjustment may conceivably mean biologically abnormal members. I must cite a case history of my early experience to illustrate the dichotomy existing between social adjustment and biologic normality. I submit it to Dr. Whitehorn as a type of conflict and social pressure which bears on the question of normality and adjustment.

Many years ago, a social worker, aged 45, brought a girl of 16 to me, the latter being in that state called unmarried pregnancy. In reality what had she done? She had simply followed the pressure of the very complicated and extremely important estral cycle. The many normal hormones got normally busy; there was an attractive young man around, and the girl followed the biologic drive established by the hormones to its normal limit. However, that biologic normality brought social maladjustment. The society in which she lived strongly disapproved and the general attitude was that she was psychopathic, an opinion in which I did not concur. I should have asked the social worker a few questions, but I admit that I did not. She was 45 years of age. Presumably, the complicated estral cycle had repeated itself several hundred times; yet she had never once followed the normal biologic drive. Socially, she was esteemed and successful; biologically, she could be simply classified as a flop.

In many other respects, human beings are asked to act quite unbiologically. For instance, a young man is strong and 20; he is studying for examinations and he looks out of a window onto a baseball park, or he sees a good-looking girl, both of which are stimuli to action. Because he is supposed to study to pass examinations for a professional career ten years or more later, he sighs or swears, or both, and goes back to his books. The golden present moment is sacrificed for a future moment. This is essential in our social-psychologic setup —essential for the success for which Dr. Whitehorn prepared his students. He asks them to sacrifice the present golden moment, though he may in his heart wish he had followed some past golden moments, himself, as I have often wished. Society imposes on us and on our biologic drives a pressure system operating through tradition and age-old institutions via praise, blame, reward and punishment. It is of the utmost importance to understand this pressure, because the question arises whether or not it is within the biologic capacity of man to live within the scope of the biosocial conflict and remain normal. A man is born with hereditary urges which date back millions of years, and within his own lifetime he must twist these drives to conform with the mores men have established in ignorant and barbaric days.

Dr. Whitehorn rightly stresses the role of competition. There is in man a will to power and aggrandizement which is real and primitive; at the same time, there is another feeling which one may call fellowship, which is as great and as important. The will to compete imposes great strain. It helps to cause inferiority (or superiority) complexes; it brings fear and competitive anguish, with questions which run the range of human competition—"Am I good-looking?" "Do I have the right nose?" "Do I speak well?" "Do I have shapely legs?" "Do I learn as well as my neighbors?" and so through the whole list of human abilities and qualities.

On the other hand, there is identification with the group which is really cooperation. This lessens competitiveness, and so one reaches what Dr. Whitehorn calls "group morale." One becomes fused with the group; and thereby competitive feeling is reduced, barriers are taken away, stresses are relieved and anxieties are lessened. In this manner, by getting away from individualistic striving, one becomes a more effective individual of the group.

What shall we aim at? How far is our present social system responsible for neuroses by emphasizing competition? How much harm is done by repressing and also pushing a child beyond his power? Can we reconcile biologic drives and social inhibitions? I could go on indefinitely, asking questions to whch the answers are beyond my horizon of wisdom.

DR. A. WARREN STEARNS: I am flattered by being asked to discuss so learned a paper. One thing I miss in it is the concept of disease. Certain balances exist in the body, one of which is temperature, another the pulse rate and another, in my opinion, the emotional life. If the temperature or the pulse rate varies, one immediately thinks of disease, but if the emotional life is out of balance, one is apt to think in philosophic terms. Common sense judgments are passed. Why is it not better to raise the question as to whether or not these persons are sick, even though the nature of the illness is still unknown? The fact that further knowledge of the nature of the sickness is needed does not make this process less desirable. The same is true of many physical diseases. Let us not forget that there is such a thing as sickness, and that in sickness normal balances are disturbed. Sickness may be an adequate explanation of the imbalance, whether it is in body temperature or in emotional life.

DR. JACOB E. FINESINGER: Dr. Whitehorn's paper is extremely stimulating. I should like to dwell on one aspect. There is no doubt that these social factors exist and that changes in them may precipitate a variety of pathologic reactions. One wonders about the personality factors involved. Not every soldier breaks down when the group morale shifts. Symptoms probably occur only in certain soldiers. The nature of the soldier's identification with the group is significant and may play a role in determining whether the soldier breaks or does not break. I believe that the mechanism of identification is important in the civilian neuroses as well. In the treatment situation, the capacity of the patient to identify with the doctor's goals may play a role in determining the success or failure of treatment. The capacity of the physician to identify with the patient is a factor in the development of the appropriate therapeutic contact. More specifically, in insight therapy this capacity of the doctor may determine the nature of the patient's productions. I should be glad if Dr. Whitehorn would speak further on the role of personality factors in the reaction to social pressures. Is it conceivable that persons with patterns of adequate adjustment can withstand a great deal of social frustration and still function normally?

DR. JOHN C. WHITEHORN: I feel a little like a school boy who has been brought up to have his teachers scold him. I have had the honor to be instructed by several who have spoken here. I particularly squirmed under some of the adjectives—"erudite" was one. I thought I had successfully avoided that insinuation. The paper was intended to be a discussion of considerations which were forcibly brought to my mind by empiric observations during the war on the incidence of neuropsychiatric illness in the troops. I disagreed with Dr. Stearns's implication that the study was speculative rather than realistic. There is a considerable body of empiric observations relating morale to neuropsychiatric casualties. What Dr. Stearns did was to point out that in an hour's discussion I did not adequately cover the subject of psychiatry. I was tempted to try to live up to the implications of erudition by citing a paragraph in Descartes' "Geometry." I cannot quote it accurately from memory. The substance of it was brought to mind by Dr. Myerson, when he took up where I had left off and carried on the discussion. Descartes closes his treatise on analytic geometry by saying that he refrained from making further applications of these interesting principles so that he would not deprive his reader of the great pleasure of making his own applications.

PHILADELPHIA NEUROLOGICAL SOCIETY

Anthony S. Tornay, M.D., *Presiding*

Regular Meeting, April 25, 1947

Membranous Obstruction of Aqueduct of Sylvius (Internal Hydrocephalus) Producing Syndrome of Midline Cerebellar Tumor. DR. WALTER G. SCHEUERMAN (by invitation) and DR. ROBERT A. GROFF.

A woman aged 23 had at the age of 17 the onset of attacks of momentary unconsciousness. At the age of 22 she began to complain of vertigo and noticed difficulty in walking. These symptoms progressed until she became bedridden, three weeks before her admission to the hospital.

Examination revealed that the patient was well developed but apathetic; the head was slightly larger than normal; there were bilateral papilledema of 1 to 2 D., rotary nystagmus, increase in all tendon reflexes, bilateral Hoffmann and Babinski reflexes and dyssynergia of the cerebellar type in all four extremities.

A ventriculogram disclosed dilatation of the lateral and third ventricles. At operation, a thin membrane was observed completely blocking the posterior end of the aqueduct of Sylvius. The membrane was removed, and recovery was uneventful. Follow-up examinations two months after operation showed that all symptoms and signs were subsiding.

DISCUSSION

DR. SAMUEL ZERITSKY: Three phenomena were mentioned as presenting symptoms: (1) prominence of the left eyeball, (2) a hissing sound within the cranium audible to the patient and (3) attacks of unconsciousness. With reestablishment of ventricular patency were these symptoms alleviated? In particular, can Dr. Scheuerman give a pathophysiologic explanation for the presence of the proptosis and the subjective hissing sound, in view of the actual operative findings?

DR. BERNARD J. ALPERS: What was the microscopic appearance of the membrane? Was a specimen obtained; if so, what was the pathologic picture?

DR. RUDOLPH JAEGER: Recently I had a case in which a cystic protrusion through the aqueduct appeared on first glance to be a diaphragm across the canal. Deeper exploration showed that the lesion was only part of a deeper-lying cyst wall. It is possible to be misled regarding the true nature of a lesion of this type in this inaccessible location.

DR. MICHAEL SCOTT: I wonder whether the obstruction in the case just presented could have been by a herniating portion of a cyst of the third ventricle which lodged in the upper portion of the dilated aqueduct. When this "membrane" was ruptured, the cyst collapsed and permitted the immediate flow into the aqueduct of ventricular fluid from the lateral ventricles. I say this because the ventricles shown are well outlined and there is no air in the third ventricle. I assume that the usual roentgenograms were taken after the air was injected, and this failure to visualize the third ventricle makes one strongly suspect a lesion in this area.

DR. JOSEPH C. YASKIN: This case is interesting and important from a practical standpoint. When I saw this patient over a year ago I felt that she had a congenital lesion but did not know its nature. I have never seen a case like this before, but I understand that similar cases have been reported, especially by Dandy. It is best to make the diagnosis is such cases before the development of papilledema, in order to avoid invalidism. An early diagnosis can be arrived at if one keeps the possibilities of congenital lesions in mind, even though one cannot be certain without exploration. The patient's condition was quite satisfactory when she left the hospital.

DR. WALTER SCHEUERMAN: In answer to Dr. Zeritsky's question: The patient did not experience the hissing sound in her head when we examined her. This, she said, became much less prominent when the vertigo began. We observed her for only about one month while she was in the hospital. She had no spells during that time. At the time of discharge she still had severe ataxia. We shall have a follow-up report at some future date. We did not obtain a specimen of the tissue, about which Dr. Alpers asked, but only punctured the cyst. This was probably a mistake from the pathologic point of view, as we do not know from where this tissue was derived. Dr. Jaeger's comments raise the question of accurate diagnosis. This lesion could not have been a cystic glioma, for before we punctured the membrane we injected dye into the lateral ventricle and saw the blue fluid immediately behind the membrane. Dr. Scott has also questioned the diagnosis. It was not a cyst of the third ventricle, because it was clearly seen that the membrane was attached to the wall of the aqueduct at the point where it was stretched across. The third ventricle did not fill, for technical reasons. It was probably incompletely drained. As to the prominence of the eyeball, about which Dr. Zeritsky asked, this observation was made by Dr. Yaskin at his examination in 1945, but was not made by us.

Aneurysm of the Internal Carotid Artery with Normal Arteriogram: Report of Two Cases. DR. BERNARD J. ALPERS and DR. JAMES J. RYAN.

The diagnosis of aneurysm involving the cerebral arteries is often based on relatively typical clinical findings. Experience with over 60 verified cases of aneurysm has indicated that the diagnosis is based on two factors: (1) the history of recurrent bouts of head pain, usually unilateral and often frontal or supraorbital, and (2) the development of progressive or acute paralysis of cranial nerves, associated often with head pain and involving chiefly one or more of the oculomotor nuclei. So characteristic is this clinical picture in our experience that its occurrence in 2 suspected cases of cerebral aneurysm led to exploration for this disorder, despite negative evidence in the arteriograms. It is these 2 cases which we wish to report at this time.

REPORT OF CASES

CASE 1.—G. O., a white girl aged 19, was admitted to Jefferson Medical College Hospital on Feb. 20, 1946, complaining of headache. She had suffered from intermittent headaches about twice a month for several years. A month before admission she complained of diplopia and inability to move the right eye inward, and in a few days she was unable to raise the right eyelid. Six days before admission she experienced sudden, excruciating pain in the top of the head and pain radiating down the back of the neck and to both shoulders. Neurologic examination revealed evidence of paralysis of all oculomotor nerve functions. Except for a slightly unsteady gait, the rest of the examination revealed nothing unusual. It was thought that the patient had an extramedullary process compressing the right oculomotor nerve. Meningioma of the sphenoid ridge and aneurysm involving the posterior communicating artery were considered. There was no roentgenologic evidence of increased intracranial pressure. When an arteriogram showed no evidence of abnormality in the vascular tree, an air encephalogram was made. This revealed a normal ventricular system, but there was no filling of the chiasmatic cistern. A craniotomy flap over the right frontal lobe was turned, and a fusiform aneurysm of the internal carotid artery, 1 cm. in diameter, was found. After ligation of the internal carotid artery, clips were placed both central and distal to the aneurysm. The patient made an uneventful postoperative recovery.

CASE 2.—A. L., a 60 year old Negro woman, was admitted to Jefferson Medical School Hospital on Feb. 26, 1946, complaining of drooping of the left eyelid and inability to move the left eyeball inward. She had had no headache, unsteadiness of gait or disturbance of consciousness. A month before admission she awoke one morning to find that the left eyelid was half closed. In the following week the lid became completely ptosed. Neurologic examination revealed, in addition to complete ptosis of the left eyelid, dilatation of the left pupil and paralysis of upward, downward and inward movements of the eyeball. It was thought that the patient probably had an aneurysm of the left internal carotid or the posterior communicating artery. Even in the presence of a normal arteriogram, a bone flap was turned over the left frontal lobe and the chiasmal area explored. A saccular aneurysm of the left internal carotid artery was encountered, but it was impossible to uncover it completely, as it adhered to the edge of the tentorium and spread beneath it. Silver clips were placed on the carotid artery distal to the aneurysm. Pulmonary edema developed three days later, and the patient died. Permission for autopsy was not granted.

COMMENT

The diagnosis of cerebral aneurysm is possible either (1) before or (2) after rupture of the aneurysm. The diagnosis after rupture is relatively simple and is based chiefly on evidences of hemorrhage into the subarachnoid space, with all the orthodox signs of meningeal irritation, and indications of paralyses of the cranial nerves, against a background of recurrent headache. In these circumstances there is relatively little difficulty in arriving at a diagnosis. The differentiation is between miliary aneurysm and aneurysm of a larger variety, of either a saccular or a fusiform type. The problem of diagnosis before rupture is more pertinent and practical, since the possibility of help to the patient is considerably greater if an aneurysm can be recognized and localized before rupture occurs.

Experience has made it clear that the large aneurysms involving the cerebral arteries can be recognized on the basis of clinical signs alone, the latter depending chiefly on the location of the aneurysm. A cerebral aneurysm should be suspected when there is a history of recurrent unilateral pain in the head or pain behind the eyeball, particularly if, after a time, there develops ocular paralysis, diplopia, facial pain, dysphasia or other symptoms of involvement of the cranial nerves. The series of events briefly outlined here is, in our experience, so characteristic of aneurysm that we have come to regard the diagnosis as possible in most instances without benefit of arteriogram or pneumogram. We were led to advise exploration in the 2 cases reported despite negative arteriographic evidence, and in both aneurysm was demonstrated. These cases demonstrate that the clinical picture of aneurysm is sufficiently characteristic to make diagnosis possible in most cases without an arteriogram. In the unusual cases in which a typical clinical picture is presented and the results of arteriography are negative exploration is justified.

DISCUSSION

DR. RUDOLPH JAEGER: This excellent presentation emphasized the fact that the diagnosis of these lesions must be made on a clinical basis and that one must not depend on the arteriograms entirely because they are often misleading, and in some instances dangerous. It is probably safer, when the clinical diagnosis has been made on such evidence as that presented in these 2 cases, to perform a craniotomy. One can ligate the internal carotid artery safely provided it is not

arteriosclerotic and there is adequate collateral circulation through the circle of Willis. I believe that when a vessel enters on one side of an aneurysm and comes out on the other side the blood mixes within the aneurysm, but when the main stream of the vessel does not pass directly through the aneurysm the latter may not fill with the contrast medium. Some large aneurysms are almost filled with clots.

DR. MICHAEL SCOTT: Over a year ago my colleagues and I saw a patient who had a spontaneous subarachnoid hemorrhage with no localizing signs except ringing in the right ear. The patient recovered and was discharged, and a few months later he returned to the hospital with recurrence of hemorrhage and complete paralysis of the right third cranial nerve. An arteriogram did not visualize the aneurysm. Nevertheless, the common carotid artery was ligated, and the patient made a complete recovery, which he has maintained. He still has ringing in the right ear at times. Since in most such cases the common carotid artery must be exposed for ligation, I see no objection to proceeding with an arteriogram at the same time.

DR. FRANCIS C. GRANT: I should like to ask Dr. Jaeger, Dr. Alpers and Dr. Ryan about the effects of ligation of the internal carotid artery in the first case. Did the patient have hemiparesis?

DR. RUDOLPH JAEGER: She did not have hemiparesis. One can ligate the internal carotid artery safely provided it is not arteriosclerotic and there is adequate collateral circulation through the circle of Willis.

DR. MICHAEL SCOTT: There is no assurance that, although the Matas compression test is done with no immediate hemiplegic effects, a paralysis will not occur on the opposite side, even three or four days after the carotid artery has been completely ligated. Therefore I do not believe that this test can definitely rule out cases in which late hemiparesis will develop. Obviously, if immediate weakness or hemiplegia develops after compression of the artery, ligation is contraindicated.

DR. FRANCIS C. GRANT: One cannot tell whether one is going to have complications or not. In my opinion, ligation cannot be decided on lightly.

DR. GEORGE D. GAMMON: May I ask Dr. Ryan why he thinks the aneurysm did not fill?

DR. JAMES J. RYAN: I shall answer Dr. Grant's question first. With regard to the tying off of the internal carotid artery, my feeling is that a situation as serious as aneurysm of the artery requires serious measures, and whether or not hemiparesis will develop is not the main issue. Thus far, the great majority of patients have had no motor weakness. In the case of the girl presented here, there are as yet no abnormal motor signs fourteen months after operation. She is still alive and doing fairly well. I cannot answer Dr. Gammon's question.

DR. MATTHEW T. MOORE: While it is true, as Dr. Ryan has said, that cerebral aneurysms have the peculiarly disagreeable potentiality of rupturing, not all do. In 1931, I had occasion to see a girl of about 16, in the outpatient department of the Temple University Hospital, who presented paralysis of the oculomotor nerve. At that time the exact nature of the lesion was not known. The patient is still alive, and it has been definitely established that she has a large aneurysm of the internal carotid artery. Thus, over a period of sixteen years this aneurysm has not ruptured and the patient is very much alive.

Irritating Effect of Iodized Vegetable Oils on the Brain and Spinal Cord.

DR. RUDOLPH JAEGER.

Experiments were made on dogs to test the tolerance of the subarachnoid space, brain and spinal cord to emulsions of iodized poppyseed, peanut and corn oils. The emulsion was prepared by forcing a mixture of 50 cc. of iodized oil, 50 cc. of isotonic sodium chloride solution U. S. P. and 5 grains (0.325 Gm.) of acacia powder through a high pressure homogenizer. This produced a stable emulsion with oil particles from 1 to 12 microns in diameter. After the emulsion was autoclaved, tested for free iodine and adjusted to the p_H of spinal fluid, small quantities were injected into the ventricle, cisterna magna and spinal canal of a number of dogs. As a standard dose, 1 cc. of the prepared emulsion was injected for each 10 pounds (4.5 Kg.) of body weight.

Some of the dogs died during the first twenty-four hours. Others died at the end of fourteen days, while a few became very sick and were killed after two weeks. All the brains showed a pronounced inflammatory reaction at the site of injection and throughout the entire subarachnoid and ventricular system. All the material used in the tests was controlled by injecting each alone into the cisterna magna of dogs. Apparently, the irritating effect of the emulsion is due to the physical nature of the fine particles of oil.

The results of these experiments point to the possible reason for occasionally observed irritating effects of the commonly used iodized oils. It also emphasizes the importance of removing these oils when possible, after diagnostic subarachnoid injection, for it has been shown that small particles of these oils break free from the main mass of oil when they are injected.

DISCUSSION

DR. A. M. ORNSTEEN: Dr. Jaeger has spoken of the ill effects of the iodized oils on the dog. He did not say anything about similar effects on human subjects. I wonder whether he has any concrete evidence of such effects on any of his patients; if he has, would he express his opinion on this evidence?

DR. MICHAEL SCOTT: I should like to ask Dr. Jaeger whether he has any explanation of why some persons have a severe reaction to iodized oil U. S. P. and others apparently have none. Would he feel that a skin test for sensitivity to iodine, before the oil is injected intraspinally, would be of any value?

I should like to discuss the question of the complete removal of pantopaque® (ethyl iodophenylundecylate) from the spinal canal. It is frequently claimed that pantopaque® can be completely removed from the spinal canal, and I think that it can in many cases. On the other hand, it is strange that the same authors write on the ease of complete removal of pantopaque® and on the rate of absorption of the mediums from the canal.

Finally, I can see no reason to condone the use of pantopaque® or any radiopaque substance for the determination of complete block in the spinal canal. If a Queckenstedt test shows a complete block, it is necessary only to inject 10 to 15 cc. of air, which is entirely innocuous and will show the level of the lesion.

DR. RUDOLPH JAEGER: In answer to Dr. Ornsteen's question about the ill effects of iodized oil on patients: There is quite a bit about this in the literature, and I have seen a number of instances in which the oil has caused definite irritation. I have seen matting of the cauda equina, particularly after I have removed the material surgically. With iodized oil U. S. P. this has often happened in years past. My colleagues and I formerly used this iodized oil to make the diagnosis of a tumor of the spinal cord. We would open the dura and try to

remove the oil at operation, after removing the tumor or the disk. This procedure, in particular, was followed by terrific matting. I think the reason is that, in the attempt to remove the material, as pointed out by Walker and Morovitz, blood is spilled into the spinal fluid and in the mopping around one breaks up the oil into fine particles. Human serum is a good emulsifying agent for iodized oils. I have seen tumors of the spinal cord produce caudal neuritis, and I have had to take out the oil. This happened in at least 4 or 5 cases. In our experience, we have had the least trouble with iodized oil U. S. P. when we have not followed through with surgical manipulation.

As shown in 1 of the dogs, the animal's subarachnoid space can be almost filled with the iodized oil, without producing any ill effects, so long as the oil is not emulsified or there is not some added irritation of the pia-arachnoid. Dr. Scott asked why some patients have a reaction to pantopaque® or iodized oil. They have slight fever, the temperature perhaps reaching 100 or 101 F. for twenty-four hours and becoming normal on the second day. This reaction has been commoner with iodized oil than with pantopaque.® I expected the reverse. I think it is the mechanical irritation of the small particles of oil into which the material may be broken up that causes the intense reaction. Pantopaque® is extremely stable. One can do almost anything with it, with dissociating the iodine from the oil. As nearly as I can learn, the absorption rates of pantopaque® have been determined on dogs. Dogs go around with their noses dependent; the anterior part of the cranial cavity is down. Dogs have been shown to have rapid excretion of the cerebrospinal fluid. Naturally, in the dog the pantopaque® is dependent in the olfactory regions, and this animal may get rid of it much more quickly than does man. In the cases I have followed, in which the medium was in the spinal dural sac, I could note no great absorption of pantopaque.® Of course, we have not been using it very long. Possibly it is absorbed when injected in 3 cc. lots, but I should prefer to remove it. I believe that it may not be absorbed as fast as one has been led to believe. Pantopaque® is a material that one can practically always remove. In my experience it gives a better myelogram than air.

I like to use a contrast medium to show me precisely where a spinal lesion is and its extent. I think it gives a better surgical approach to the lesion, and I can see no objection to using pantopaque,® for it can be removed.

Spasmodic Torticollis: Successful Surgical Treatment. DR. HENRY WYCIS.

The anatomic and neurophysiologic basis of torticollar movements of the neck were briefly reviewed and discussed. The case of a woman, aged 35, who had had spasmodic torticollis for four years prior to operation was presented. The patient had received osteopathic, orthopedic and psychiatric treatment, without relief.

A high cervical laminectomy was performed, and both spinal accessory nerves were divided intradurally. The anterior roots of the first, second and third cervical nerves were likewise divided intradurally. The posterior roots were spared.

The patient made a complete recovery, and at the time of this report, two years after operation, she was entirely free of any spasmodic movements. Movements of the neck were limited, but not entirely lost.

DISCUSSION

DR. RUDOLPH JAEGER: I have performed this operation perhaps half a dozen times, but I must say I have not had the happy results obtained in this case. I think, therefore, as Dr. Wycis has said, that not all persons have the same number of muscles or involvement of the same muscles. If the patient's

upper cervical muscles are largely involved, this operation will work out well. My operative results have been so poor that I hate to see people come for the operation, and I discourage them from having it. Dr. Wycis should be complimented on his results. He saved this woman from a devastating disease. He has selected the right patient and the right operation.

DR. FRANCIS C. GRANT: The result in this case is by far the best that I have seen. Dr. Frazier from 1925 to 1930 operated on 11 patients with this condition. The results were unfortunate. Four had fairly satisfactory results, but the other 7 are dreadfully unhappy. Their necks are twisted about, and it is hopeless to do anything for them. One should be as certain as possible that the torticollis is not an early dystonia, because if such is the case the result of any operative procedure may be completely nullified by the spread of the dystonia. The satisfactory result in Dr. Wycis' case makes one wonder whether neurologists have not been too conservative in the past.

DR. MICHAEL SCOTT: Dr. Wycis and I operated together in another case, of a more advanced type, with twitching movements of the ocular muscles, and the results were not so satisfactory as in the case he has reported here.

Approximately one year ago I examined a patient who had been operated on by Dr. Walter Dandy five years before for spasmodic torticollis. The development of pain in the back of her neck was the reason for my examination. I questioned the patient at length concerning her symptoms before and after the operation; Dr. Dandy had apparently secured an excellent result in her case. There was a midline cervical incision, as well as an incision over both the sternocleidomastoid muscles; I assumed, therefore, that he had cut the anterior roots in the cervical area and the spinal accessory nerves in the neck. Her only complaint was stiffness in the back of her neck at times.

DR. A. M. ORNSTEEN: It is not my intention to belittle the credit justly due Dr. Wycis for the excellent results he obtained in this case; as a matter of fact, if I were confronted with a similar problem and could be assured of such a result, I should have him operate on the patient. But I would emphasize what Dr. Grant has already said about the possibility of the torticollis in this instance being a fragment of dystonia which may in the future spread to other parts of the body. The surgical results in cases of torticollis are not uniformly good, and rarely are they as strikingly successful as in Dr. Wycis' case; I wonder, therefore, whether psychotherapy was not a factor in the result. It is well known that a surgical operation is sometimes very effective psychotherapy. Perhaps a thoroughgoing psychiatric study of this woman might bring to light psychogenic factors which would serve to differentiate her condition from dystonia.

DR. JOSEPH C. YASKIN: For practical purposes, torticollis should be divided into several groups. There is a type of fixed torticollis due to disease, often congenital or traumatic, and affecting the muscles responsible for the torticollis. This type often presents an orthopedic problem. The second type is the so-called spasmodic torticollis, which, again, can be subdivided into two categories: the type which is definitely organic, in that in the course of time involuntary movements develop in other parts of the body, proving the process to be a disease of the basal ganglia, and the type in which the torticollis remains localized and the etiologic diagnosis is difficult. In the course of years I have come to believe that the localized type of torticollis is often organic in origin, even though it responds poorly to almost any form of surgical treatment. On the other hand, there is no doubt in my mind that there are some cases of spasmodic torticollis of psychogenic origin which yield to psychotherapy. I have seen several such

cases. One is of particular interest, since the patient came to me with a severe spasmodic torticollis and after psychotherapy made a complete recovery. However, a few months later, he wrote from a western state that he wished he had a return of his torticollis and the disappearance of his severe anxiety, which had since developed.

Another patient, whom I regarded as having psychogenic torticollis, improved greatly and with the onset of World War II went to France and became completely well. He was joined by his wife and some months later became disturbed over the fact that she was overly friendly with some of the officers in the armed forces. He then had a recurrence of his condition, which was rather resistant to further treatment, but so far as I know he is again quite well.

I was much interested in Dr. Wycis' demonstration. He is to be congratulated that there has been so little loss in muscle power, a condition I never observed after operation in previous cases.

DR. ELI MARKOVITZ: I should like to ask Dr. Yaskin whether in those patients with psychogenic torticollis whom he has seen, the mechanism was hysterical or of some other type, such as a compulsive response.

DR. JOSEPH C. YASKIN: No, the cases I have studied did not reflect hysterical reactions. They were, rather, of the compulsive-obsessive type. The occasional twitching of the neck in a hysterical patient is vastly different from the complex physiologic pattern exhibited in cases of torticollis, even as the psychopathology of hysteria is vastly different from that of the compulsive-obsessive reactions.

DR. HENRY WYCIS: I should like to make one point definite. I did cut both spinal accessory nerves intradurally. The ability which the patient has to shrug the shoulders may be due to the intact nerve supply of the levator anguli scapulae.

Dr. Jaeger mentioned that in many cases operation is not successful because the involvement of musculature is too extensive. I wholly agree with his opinion; if the numerous muscles are involved bilaterally, with associated dystonia, the surgical result will be poor.

With regard to psychiatric treatment, I should like to say that the psychiatrists were given a fair chance in this case, and the patient was referred to me after the psychiatric treatment had failed.

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